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Review Article

Decline in prolonged hormone replacement therapy in women aged 45 years or more, and impact of a centralised database tool

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REZUMAT

Obiectv: Evaluarea întreruperii administrării în utilizarea prelungită a terapiei de înlocuire hormonală (HRT) în perioada de menopauză și post-menopauză în Olanda, după publicarea studiului „Million Women" în revista *The Lancet* din 9 august 2003. În continuarea acesteia a fost facută o estimare a contribuției unei baze de date-instrument centralizată, pentru a ajuta farmaciștii și pacienții acestora care urmează o terapie HRT prelungită.

Încadrarea studiului: Datele dispersate din mai mult de 90% dintre farmaciile olandeze au fost colectate în baza de date centralizată. La scurt timp dupa publicarea studiului „Million Women", această bază de date a fost folosită pentru a oferi comunității farmaciștilor acces online la listele pacienților care urmau HRT prelungit.

Metoda: În august 2003, toate femeile care au utilizat HRT pe durata de cel puțin un an au fost selectate ca utilizatori pe termen lung ai terapiei respective. Acest grup a fost monitorizat până în aprilie 2004. Proporția de paciente care au întrerupt terapia prelungită HRT a fost calculată. Această diminuare a fost de asemenea măsurată în acord cu utilizarea bazei de date-instrument. În acest scop, comunitatea farmaciilor a fost divizată în două grupe: farmaciile care au consultat des baza de date centralizată (farmacii T; n=343) și farmaciile care în mod evident nu au consultat acest instrument (farmacii C; n=490). Cele două grupuri de farmacii au fost comparate în concordanță cu acele caracteristici ale unei farmacii în care informațiile erau disponibile într-o bază de date centralizată. Au fost de asemenea comparate în ceea ce privește caracteristicile pacienților care erau colectați în mod normal în baza de date. Diferențele dintre cele două grupuri pentru valorile medii ale acestor parametri erau măsurate prin testul lui „chi pătrat" pentru trendul variabilelor ordinale cu mai multe categorii. Proporția pacientelor care au oprit tratamentul HRT prelungit a fost calculată pentru ambele grupe de farmacii. Aceste proporții au fost comparate cu un test Z pentru proporții. Cele două grupuri de farmacii au fost comparate pentru întreruperea tratamentului HRT și pentru întreruperea lui prematură cu ajutorul unei curbe statistice. Alte tipuri de analiză au fost utilizate pentru a estima șansele întreruperii tratamentului cu HRT la pacientele din ambele grupuri de farmacii, cu posibilitatea de a adapta acest lucru la vârsta pacientei sau la tipul de medicație HRT.

Ce a reieșit din acest studiu: După publicarea studiului „Million Women" în revista *The Lancet* din 9 august 2003, 63% dintre femeile din Olanda care au folosit terapia HRT pe o durată mai mare de un an în august 2003, au întrerupt utilizarea prelungită a acesteia în aprilie 2004.

O bază de date-instrument centralizată, care să ofere comunității farmaciilor o listă cu pacientele lor care urmează o terapie HRT prelungită, a dus la o proporție mai mare a întreruperii terapiei în grupul T al farmaciilor, decât în grupul C (65% față de 62%). În continuarea acestui studiu, timpul necesar pacientelor cu terapie HRT prelungită a fost mai scurt în mod semnificativ în cadrul grupului T, decât în cel C (187 zile față de 202 zile). Pacientele din farmaciile T au o șansă semnificativ mai mare, de 7,6%, de a întrerupe tratamentul lor cu HRT mai devreme.

Concluzii: Rezultatele studiului „Million Women" au avut un impact major în utilizarea terapiei HRT în Olanda. O bază de date-instrument centralizată pentru utilizarea pe termen lung a HRT poate avea un impact semnificativ în modele utilizate în distribuție.

ABSTRACT

Objective: Evaluation of discontinuation in prolonged use of menopausal and post-menopausal hormone replacement therapy (HRT) in The Netherlands after the publication of the Million Women Study in *The Lancet* of August 9, 2003. Furthermore estimation of the contribution of a centralized database tool on this decline, supplying community pharmacists with their patients on prolonged HRT therapy.

Setting: Dispensing data of more than 90% of Dutch community pharmacies were collected in a centralized database. Shortly after the publication of the Million Women Study, this database was used to offer community pharmacists online access to a listing of their patients with prolonged HRT use.

Methods: In August 2003 all women who had used HRT for at least one year were selected as long-term users. This cohort was followed until April 2004. The proportion of patients who had stopped their prolonged HRT in this cohort was calculated. This decline was also measured according to the use of a database tool. For this purpose community pharmacies were divided into pharmacies who had repeatedly consulted the centralised database tool (T pharmacies; n=343) and control pharmacies who had evidently not consulted the tool (C pharmacies; n=490). The two groups of pharmacies were compared according to characteristics of the pharmacy on which information was available in the centralised database. They were also compared for patient characteristics that were routinely collected in the database. Differences between the two groups for averages of these parameters were tested with a chi square test and with a chi square test for trend for ordinal variables with more categories. The proportion of patients who stopped their prolonged HRT was

calculated for each of the two groups of pharmacies. These proportions were compared with a *Z* test for proportions. The two groups of pharmacies were compared for cessation of HRT treatment and for ceasing treatment earlier by a Kaplan–Meier survival curve. Cox survival analyses was used to estimate the chances for discontinuation of HRT for patients within the two pharmacy groups with the possibility to adjust for possible confounders such as patient's age and type of HRT medication.

Key findings: After publication of the Million Women Study in *The Lancet* of August 9, 2003, 63% of the women in The Netherlands who had used HRT for more than one year in August 2003 had stopped their prolonged use in April 2004. A centralised database tool supplying community pharmacists with a list of their patients on prolonged HRT therapy caused a significantly higher proportion of cessation in the T group of pharmacies than in the C group (65% versus 62%; *P* < 0.05). Furthermore, the time needed for halving the number of patients on prolonged HRT was significantly shorter in T pharmacies than in C pharmacies (187 days versus 202 days; *P* < 0.05). Patients in T pharmacies had a significantly increased chance of 7.6% (95% confidence interval: 1.05–1.10) of discontinuing their HRT and of doing so earlier.

Conclusions: The results of the Million Women Study had a major impact on prolonged HRT use in The Netherlands. A centralised database tool for prolonged use of HRT could have a modest but significant impact on dispensing patterns.

INTRODUCTION

In The Netherlands, all dispensed prescriptions for outpatients are recorded in the computer systems of community pharmacies. The Foundation of Pharmaceutical Statistics (SFK) collects these data from 90% of the community pharmacies (1540 of 1700), and thereby covers 13.5 million of the 16 million inhabitants of The Netherlands. To safeguard privacy, the SFK gathers these data in an anonymous format, but each dispensing record contains a patient code, which is used in the local computer system to identify that particular patient. This allows the SFK to reconstruct utilization patterns of individual patients, without any possibility of identifying the patient other than going back to the local computer system itself. The SFK database was initially set up to promote political and economic interests of Dutch pharmacists, but this wealth of data is equally useful for monitoring the dispensing of medicines over time, and in relation to new evidence for effects and side-effects of medication.

Furthermore this database can be used to improve the pharmaceutical care that pharmacists provide to their patients. For several years, the Scientific Institute Dutch Pharmacists (WINAp) has been designing search strategies that target chronically sick patients in the SFK database who have a drug dispensing profile suggestive of suboptimal drug therapy according to guidelines. The relevant patient codes are fed back online to the community pharmacies that supplied the original data, together with evidence-based advice on how the drug therapy of those patients could be improved. In this study the database was used to analyse the effect of the Million Women Study (MWS) on the use of prolonged hormone replacement therapy (HRT).1 This large study was published in *The Lancet* of August 9, 2003. It showed higher relative risks for breast cancer in users of HRT than was found in earlier randomised trials and meta-analyses. (2–4) These increased risks were observed sooner than before and involved not only oestrogen/progestagen combinations but also oestrogens only and tibolone. This prompted the Dutch Society of General Practitioners to issue a warning against the prolonged use of HRT by menopausal and post-menopausal women. (5) WINAp and SFK responded within days with the development of a search strategy for women aged 45 years or more who were current users of HRT and had been users for at least one year. The HRT search provided community pharmacists with lists of their own eligible patients, which could be accessed online through a personal password on the web server of the SFK. The pharmacist could arrange these data into separate lists of patients for each general practitioner (GP) and the Dutch Society of General Practitioners drew the attention of its members to the availability of this pharmacists' service. Since the beginning of the 1980s it has become increasingly common in The Netherlands for community pharmacists to meet regularly with GPs in pharmacotherapy circles. Here the quality of prescribing is discussed, based on actual dispensing data from the pharmacies. (6) In general these data have to be selected by the pharmacists. Data selection can be quite time consuming for pharmacists, certainly when patients have to fulfil certain preconditions such as prolonged use of medication In this case, the HRT search was a particularly convenient tool for pharmacists.

The first purpose of this study was to evaluate the impact of the Million Women Study on prolonged HRT use in The Netherlands. Secondly we wanted to investigate to what extent the availability of the HRT search contributed to the decline of prolonged HRT use from August 2003 to April 2004.

METHODS

Sample
Selection of pharmacies
All pharmacies for which the SFK had complete dispensing data sets from April 1, 2002 to April 1,

2004 were selected. Medication history a year prior to August 1, 2003 was necessary to be able to select patients with prolonged use of HRT at the beginning of the study period.

In order to compare the effect of the centralised database tool, pharmacies were divided into two groups: one group that had consulted the HRT search on the SFK website at least five times were regarded as users of this database tool (T pharmacies). As a control group (C pharmacies) pharmacies were selected that had not visited the web page offering the HRT search even once during the study period. Pharmacies that had visited the HRT web page just one to four times were excluded from further analysis, because it could not be ascertained if they had looked only superficially or really used the available listings for an intervention. Differences between these two groups of pharmacies were compared according to basic characteristics on which information was available in the centralised database (Table 1).

Selection of patients with prolonged HRT use at the beginning of the study period

From the included pharmacies, all women aged between 45 and 65 years who had had at least four prescriptions of HRT in the year prior to August 1, 2003 were selected. On guidance of the MWS,[1] HRT prescriptions were identified on the basis of the following codes in the Anatomical, Therapeutic Chemical (ATC) classification system:[7] G03C (oestrogens); G03DC05 (tibolone); G03F (oestrogen/progestagen combinations). Trade products with an estradiol/cyproterone combination were also included, but medicines for vaginal use were excluded. Women whose prolonged HRT use had already ended before August 1, 2003 were excluded, because they had evidently stopped for reasons other than the MWS and the HRT search. Periods of HRT use could be calculated from the number of dispensed pills divided by the daily prescribed dosage.

For the impact of the centralised database tool, the two groups of pharmacies were compared for patient characteristics that were routinely collected in the database (Table 2).

Analysis
Proportions of patients who discontinued prolonged HRT use in the Netherlands during the study period

For all selected patients with prolonged HRT use on August 1, 2003, it was determined whether they had stopped their HRT on April 1, 2004. If a period of use ended before then and had not been renewed by a new prescription, the patient was assumed to have stopped her medication.

The proportion of prolonged users of HRT at the start of the study in August 1, 2003 that had discontinued their HRT use at the end of the study period in April 1, 2004 was estimated for the whole group of patients selected in all pharmacies.

Table 1 Characteristics of the pharmacies who had used the centralised database tool (T pharmacies) and control pharmacies who had not (C pharmacies)

	T pharmacies n = 335 (SD)	C pharmacies n = 482 (SD)	Z test	χ^2; df	P
Average number of non-managing pharmacists	0.7 (0.74)	0.6 (0.68)	0.121		ns
Average sum of weekly working hours of non-managing pharmacists	21 (24)	18 (22)	0.069		ns
Average number of pharmaceutical assistants	9.1 (4.0)	8.6 (5.6)	0.19		ns
Average sum of weekly working hours of pharmaceutical assistants	242 (135)	231 (178)	0.359		ns
Average number of non-pharmaceutical employees	2.7 (4.1)	2.5 (1.9)	0.305		ns
Percentage of pharmacies within a certain degree of urbanisation[a]				0.323; 1	ns
very high (big city)	21	19			
high	32	26			
moderate	20	25			
little	22	21			
very little (village)	5	9			
Average number of delivered prescriptions in August, 2003	7532 (3268)	7209 (2850)	0.134		ns
Average number of patients in private insurance system[b]	4505 (2273)	4714 (6160)	0.553		ns
Average number of patients in National Health Service	6855 (3612)	7299 (18 123)	0.659		ns

[a]Degrees of urbanisation by the national statistical department (CBS) based on the number of addresses per region.
[b]People are obliged to join the National Health Service with an income below a certain threshold, and only persons with higher income are free to choose a private health insurance.
df, degrees of freedom; ns, not significant; SD, standard deviation.

Table 2 Basic patient characteristics in the pharmacies who had used the centralised database tool (T pharmacies) and control pharmacies who had not (C pharmacies)

	Patients in T pharmacies n = 20 442	Patients in C pharmacies n = 29 770	Z test	χ^2; df	P
Average number of long-term users per pharmacy	71 (SD = 36)	72 (SD = 35)	0.766		
Subdivided according to age (years)				0.744; 1	ns
≤ 50	3563 (17.4%)	5086 (17.0%)			
51–55	7470 (36.5%)	10 996 (36.9%)			
56–60	6864 (33.6%)	10 018 (33.7%)			
≥ 61	2545 (12.4%)	3688 (12.4%)			
Subdivided according to type of HRT				0.00; 3	s
G03C: oestrogens	7705 (37.7%)	11 440 (38.4%)			
G03DC05: tibolone	4027 (19.7%)	5355 (18.0%)			
G03F: ostrogen/progestagen combinations	8388 (41.0%)	12 412 (41.7%)			
trade products with estradiol/cyproterone	322 (1.6%)	563 (1.9%)			

df, degrees of freedom; SD, standard deviation; s, significant at $P < 0.05$; ns, not significant.

Characteristics of pharmacies and basic patient characteristics

Within the pharmacies two groups were formed according to the use of the centralised database tool. One group consisted of the pharmacies who had repeatedly consulted the centralized database tool (T pharmacies; n=343). The other group were control pharmacies who had apparently never used the database tool (C pharmacies; n=490). These two groups were compared for basic characteristics that were routinely collected within the database, such as business index numbers and characteristics of their patients. For business index numbers the number of employees, working hours, delivered prescriptions and the degree of urbanisation could be derived from the database. Patients' data relating to age, kind of HRT and type of health insurance system of the patient were available in the database. Differences between the groups of pharmacies were analysed with Z tests for proportions. Categorical data were compared using chi square tests and for ordinal variables with more categories with chi square tests for trend.

Effect of the centralised database tool

In order to estimate the effect of the centralised database tool, the proportion of those who stopped HRT therapy (stoppers) in the study cohort was estimated separately for the T and C pharmacies. The difference in mean proportions of stoppers between these groups of pharmacies was analysed with a Z test for proportions. With a Kaplan–Meier survival curve the probability of cessation of HRT treatment and of ceasing earlier was compared between the two groups of pharmacies (Figure 1). Cox survival analysis was used to adjust for possible confounders such as patient's age and type of HRT medication. SPSS for Windows (version 12.0.1),

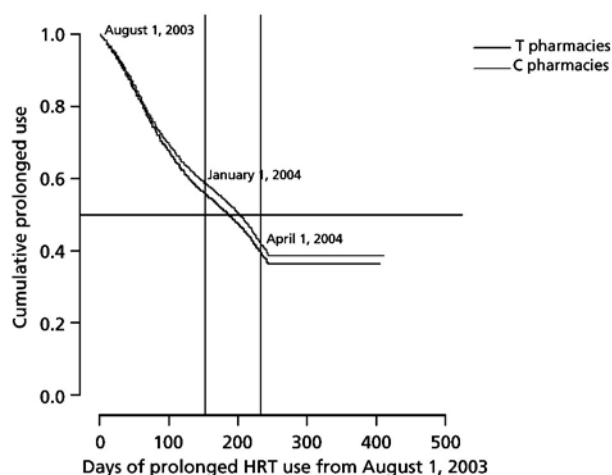Python for Linux (version 2.3.3) and DB2 for OS/400 (version V5R1) were used for these calculations.

Figure 1 Kaplan–Meier curves of survival functions for discontinuation of HRT in T pharmacies and C pharmacies.

Results

Characteristics of pharmacies and patients

A total of 833 pharmacies fulfilled all the selection criteria, 343 T pharmacies and 490 C pharmacies; 335 T pharmacies and 482 C pharmacies had supplied enough data for a comparison on general parameters. The two groups of pharmacies did not differ in the number of employees, average working hours, number of delivered prescriptions, degree of urbanisation or the insurance system of their patients (Table 1).

A total of 50 212 women from these pharmacies were identified as current users who had been users for at least one year on August 1, 2003; 20 442 women were from T pharmacies and 29 770 women from C pharmacies. The two groups of pharmacies did not differ in average number of long-term users and the age structure of their patients. Patients in T

pharmacies however used significantly more tibolone and fewer oestrogens or hormonal combinations than patients of C pharmacies (Table 2).

Proportions of patients who discontinued prolonged HRT during the study period

Sixty-three per cent of patients in The Netherlands with prolonged HRT use on August 1, 2003 had stopped their HRT on April 1, 2004. This was an average percentage of all prolonged HRT users. We also calculated proportions of women who had discontinued their prolonged HRT use within the pharmacies as percentages of stoppers at each pharmacy. The average of these results was also 63%, indicating that any group effects within patients of one pharmacy could be ignored.

Effect of the centralised database tool

The average proportion of patients who had discontinued their prolonged use of HRT was significantly higher in the T pharmacies than in the C pharmacies (65% versus 62%; $P < 0.05$).

The Kaplan–Meier survival curves for T pharmacies and C pharmacies showed that patients in the T pharmacies discontinued their HRT more rapidly than patients in the control group (Figure 1). Furthermore, the time needed for halving the number of patients on prolonged HRT was significantly shorter in T pharmacies than in C pharmacies (187 days versus 202 days; $P < 0.05$). Cox survival analysis showed that patients in T pharmacies had a significantly increased chance of 7.6% (95% confidence interval: 1.05–1.10) of discontinuing their HRT and of doing so earlier than patients in C pharmacies. Possible confounders such as patient's age and type of HRT used most recently did not influence these results (changes in outcome were smaller than 5%). The proportional hazard assumption that the probability of discontinuation remained constant during the study period proved to be valid (visual check with a LML function).

DISCUSSION

This study shows a high rate (63%) of women having stopped their prolonged menopausal and post-menopausal HRT on April 1, 2004 in response to the results of the Million Women Study. After publication of the Women's Health Initiative trial, Hersh et al. reported a rapid decline of use for two major oral oestrogen/progestagen brands in The United States: the percentage decreases were 66% and 33%, respectively. (8) Substantial rates of decline in drug therapy after publication of a large

study with unfavourable results have also been observed for cardiovascular medication in the United States. Stafford et al. examined changes in the prescribing of alpha-blockers for hypertension following the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). (9,10) The doxazosin arm of this trial had been terminated early because of unfavourable results. After its publication in April 2000, new annual alpha-blocker prescription orders declined by 26%, dispensed prescriptions by 22% and physician-reported drug use by 54%.

In general it is a limitation of our study that we did not interview the patients to verify their discontinuation of HRT use but relied completely on pharmacy records. Therefore we do not know for certain whether the women really stopped their medication or were just late in collecting their next prescription. In order to estimate the degree of potential misclassification, we calculated the number of days no longer covered by an earlier prescription on April 1, 2004. On average, women had stopped prolonged HRT for 130 days (standard deviation of 71 days); 75% of them had a period of past use of more than 65 days, and 90% had not renewed their HRT prescription for at least 22 days. These gaps in medication seem too long to be regarded as just being a bit late for renewal. A further source of misclassification could result from filling of a prescription in another pharmacy. However, this is not a major issue in The Netherlands where about 90% of patients always visit the same pharmacy. (11,12)

Use of the HRT search by community pharmacists produced a significant but modest surplus of 3% on top of the large discontinuation rate of 62% in control pharmacies. These figures correspond to an additional 1.8 stoppers to a background rate of about 38 stoppers per pharmacy.

Selection bias may have occurred by our decision to limit categorisation of T pharmacies to pharmacies with at least five visits to the SFK web page for the HRT search. This limit was chosen on the basis of previous experience with other searches, where we found that pharmacists needed to access the SFK server several times to consult both the patient listings and the background information. In the group of T pharmacies, 65% visited the web pages for the HRT search more than five times, and 45% did so even more than ten times.

As the groups of pharmacies in our study were not composed at random, a type of volunteer bias is conceivable. It is possible that the pharmacists who made use of the HRT search were more dedicated

to the provision of pharmaceutical care and were more accustomed to influencing prescription patterns of local GPs. Therefore it could be that these pharmacies would have had more impact on prescription patterns for HRT anyway. In order to gain insight into possible differences of potential confounders, we compared the data routinely collected in our database. No significant differences were observed for general parameters such as number and working hours of employees, number of delivered prescriptions or degree of urbanisation. As an approximate measure of the social status of the patients, we took the type of health insurance system, because in The Netherlands only those with a certain monthly income have a free choice for a private insurance system. This factor nevertheless did not vary between the two groups, nor did any of the other parameters we checked (Table 1).

Further we paid attention to possible differences in the patient populations. There were no differences in the average number of long-term users per pharmacy or the age structure of patients. Patients differed however slightly but significantly in their type of HRT medication. Patients in T pharmacies used more tibolone but fewer oestrogens or combinations (Table 2). The Million Women Study had shown the highest risks for HRT combinations, followed by tibolone and oestrogen- only preparations. Because of the highest risk for HRT combinations, more patients of C pharmacies should have been more motivated to discontinue their medication. On the other hand, the Million Women Study was the first study revealing an increased risk for tibolone. From this point of view, more patients of the T pharmacies had reason to discontinue their HRT use. However as can be seen from Table 2, the differences in percentages are tiny, and in our Cox regression model we could not find a significant influence of the type of HRT on cessation of HRT use. From our data we conclude the two groups of pharmacies to be comparable.

CONCLUSION

We report here the substantial rate of discontinuation of prolonged HRT use after publication of the Million Women Study. The effectiveness of a centralised database tool has to be proved by further research, when changing views about drug therapy receive less alarming and widespread coverage in professional and general media.

REFERENCES

1. Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2003;362:419–27.
2. **Hulley S, Grady D, Bush T et al** – Randomized trial of estrogen plus proegestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605–13.
3. WHI Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized trial. *JAMA* 2002;288:321–33.
4. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52705 women with breast cancer and 108 411 women without breast cancer. *Lancet* 1997;350:10–47.
5. Nederlandse Huisartsen Genootschap. NHG-Standpunt Hormoongebruik in de Overgang. nhg.artsennet.nl/index (accessed November 17, 2005).
6. **Jansen J, Van Dijk L, Wagner C, De Bakker D** – Professionalisering van het FTO in Noord-Holland Noord. Evaluatie van een pilot. *Utrecht: Nivel;* 2004.
7. Anonymous. ATC index with DDDs. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2004.
8. **Hersh AL, Stefanick ML, Stafford RS** – National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA* 2004;291:47–53.
9. **Stafford RS, Furberg CD, Finkelstein SN et al** – Impact of clinical trial results on national trends in alpha-blocker prescribing, 1996–2002. *JAMA* 2004;291:54–62.
10. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000; 283:1967–75.
11. **Klungel OH, de Boer A, Paes AH et al** – Agreement between self reported antihypertensive drug use and pharmacy records in a population based study in The Netherlands. *Pharm World Sci* 1999;21:217–20.
12. **Monster TB, Janssen WM, de Jong PE, de Jong van den Berg LT** – Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. *Pharmacoepidemiol Drug Saf* 2002; 11:379–84.