Family Practice
Vol. 17, No. 3

Printed in Great Britain

The development of polypharmacy. A longitudinal study

LJG Veehof, RE Stewart, FM Haaijer-Ruskamp and B Meyboom-de Jong

Veehof LJG, Stewart RE, Haaijer-Ruskamp FM and Meyboom-de Jong B. The development of polypharmacy. A longitudinal study. *Family Practice* 2000; **17:** 261–267.

Background. To date, only a few studies have been carried out on the development and progress of polypharmacy in relation to morbidity in general practices in The Netherlands.

Objective. The aim of this study was to investigate the relationship between an increase in long-term drug use and the incidence and severity of some chronic diseases, particularly in the elderly.

Methods. Data on medication and morbidity of 1544 elderly people were collected for the period 1994–1997 from three family practices in the medication and morbidity Registration Network of Groningen (RNG) in the northern part of The Netherlands. Polypharmacy is defined as the long-term simultaneous use of two or more drugs; long-term is defined as >240 days in a year. We looked for differences in incidences of some chronic diseases in those subgroups of the elderly in whom multiple long-term drug use respectively increased, stayed constant or did not exist. Polypharmacy at the end of the period was predicted using regression analysis.

Results. Polypharmacy occurred in 42% of the elderly at the end of 1997, with major polypharmacy (>5 drugs) in only 4%. The average number of drugs used long-term increased from 1.3 to 1.8 in 4 years. Predictors for the increase of polypharmacy were the number of drugs at the start, age, diabetes, coronary ischaemic diseases and use of medication without a clear indication ($P < 0.005$). The average number of diseases also increased, especially in the elderly who showed the greatest increase in long-term drug use; however, there was no significant difference from the groups with a slow or no increase in drug use.

Discussion. Polypharmacy showed a slow increase over 4 years: almost 20% of the elderly developed polypharmacy, i.e. going from no drugs or one drug to two or more drugs. Polypharmacy develops mainly in elderly patients who already use several drugs, who are known to suffer from cardiovascular diseases, diabetes or stomach symptoms, those who often take drugs (especially sedatives/hypnotics) without clear indication and those who develop hypertension or atrial fibrillation over time.

Keywords. Development, elderly, family practice, polypharmacy.

Introduction

Although polypharmacy is considered to be one of the problem areas which doctors have to be aware of, few studies have looked into the development of polypharmacy over time. Those that have done so have found an increase in the extent of polypharmacy over time.[1–4]

These studies, however, have used only a limited number of measurements in time, and are therefore of limited value with regard to the development of drug use over time. A more recent study found that 50% of the elderly using three or more drugs started additional treatment in the following 2 years, supporting the evidence of increasing polypharmacy over time.[5] However, the study provided little information about the underlying mechanisms of the increase in polypharmacy. There is no information about the kind of diseases contributing to an increase in polypharmacy. Longitudinal studies can provide such information and may give clues about possibilities (or the need) for interventions.

Received 6 August 1999; Accepted 21 December 1999.
Department of General Practice and Northern Centre of Health Care, University of Groningen, The Netherlands. Correspondence to LJG Veehof, Ant. Deusinglaan 4, 9713 AW Groningen, The Netherlands.

Deterioration in health status (increase in number of diseases and worsening of diseases) has been described as relevant with regard to the development of polypharmacy.[6,7] The effect of a deterioration in health also gives an indication of the limitation of what can be expected of interventions aimed at limiting polypharmacy.

Up until now, only a few studies have been undertaken on the development and progress of polypharmacy in relation to morbidity in general practices in The Netherlands. Dutch GPs are able to survey their patients' drug use; in view of medication control and medication advice, it is important for them to understand the development of polypharmacy. Tracing and observing certain high-risk groups will make supervision of drug use in general practice much easier.

In this study, we looked at the increase in polypharmacy in a 4-year period in relation to developments in morbidity, in particular the number of diseases and the kind of diseases causing polypharmacy.

Method

Study population

The study was based on a continuous database of morbidity [International Classification of Primary Care (ICPC) code] and medication (ATC code) in three general practices in the North of The Netherlands, participating in the Registration Network of Groningen (RNG). In this registration network, all symptoms, diagnoses and medications are registered prospectively and entered into a database. The study period was 1994–1997. The study was limited to 1544 elderly persons of 65 years and older for whom a complete data set over the study period was available.

Variables

Polypharmacy is defined as the long-term use of two or more drugs, long-term being defined as prescribed for at least 60 days per quarter per year. Three months seems to be a valid point-prevalence for measuring polypharmacy.[8] As a 'wash-in' period, we used the first quarter of 1994, resulting in an analysis of the development of polypharmacy starting from the second quarter of 1994. In The Netherlands, by law, prescriptions cannot be for longer than 3 months. Polypharmacy is characterized as minor (2–3 drugs), moderate (4–5 drugs) and major (>5 drugs). The development of polypharmacy has been calculated as the increase in the average number of long-term drugs used per quarter per patient, the increase being indicated by the β-coefficient over the 4-year period.

In order to get an idea of the rate at which polypharmacy develops, we compared the long-term drug use in 1997 with that in 1994. In doing so, the group that changed from no polypharmacy to polypharmacy was compared with the group that was known to have polypharmacy and also with the group which did not develop polypharmacy in the 4-year period. To gain a better understanding of the association between increase of polypharmacy and increase of morbidity, it was necessary to look into the long-term drug use and the morbidity per year for 1994 and 1997, respectively. A period of 3 months is too short to obtain a satisfactory idea of the morbidity, because patients do not necessarily have to consult their doctor concerning that particular disease, nor do they have to ask for and get prescriptions. The period for repeat prescriptions is mainly 3 months.

Inclusion criteria for morbidity were chronic diseases, clinically relevant for general practice, including: ischaemic heart disease, heart failure, atrial fibrillation, hypertension, diabetes, asthma/COPD, psychiatric diseases (such as dementia and other psychoses), diseases of the oesophagus, stomach and duodenum, feeling depressed and depression, vertigo and osteoarthritis/arthropathy (including rheumatoid arthritis and osteoporosis). Earlier studies have shown that the physician does not have a clear indication of many of the drugs taken by the elderly.[9] The use of drugs without proper indication is found frequently in polypharmacy. This concerns mainly the use of sedatives/hypnotics (65%), laxatives (8%), antidepressants (5%) and analgesics (4%).[10] Diseases were classified according to the ICPC; for the use of medication without clear indication, a special ICPC code (P18) was used.[11] The medication was classified according to the ATC classification.[12]

Deterioration in health was measured by the incidence of disease episodes between 1994 and 1997, indicating the increase of all disease episodes of care per patient. A disease episode of care is the development of a disease from the moment a patient presents with it to the doctor to the end of the medical care for that problem.[13]

As a second indicator of deterioration in health, we used the proportion of house calls in all face-to-face contacts, assuming that a deterioration in health is usually accompanied by an increase in house calls.

Analysis

The relevance of morbidity in the development of polypharmacy was analysed comparing the incidence over the 4 years of the selected diseases for patients whose drug use increased from no polypharmacy (0–1 drug) in 1994 to polypharmacy (≥2) in 1997 ($n = 293$) with those whose drug use stayed the same throughout the whole period, i.e. the group with no drugs or one drug ($n = 843$) and the group that used two or more drugs over the whole period ($n = 341$). In the group with an increase of polypharmacy, we distinguished patients ($n = 41$) with a large increase (from 0–1 to >4) and those ($n = 252$) with a smaller increase (from 0–1 to 2–4). By means of variance analysis, the mean differences in disease episodes, face-to-face contacts and percentages of house calls were assessed. By means of multiple regression analysis, we assessed the predictive value of age, sex, chronic diseases and combinations of these already

existing at the start of the research, with regard to polypharmacy at the end of the period.

Results

Polypharmacy was found in 634 persons in the cohort (n = 1544) at the end of the 4-year research period, and in 408 persons at the beginning of the research. The average age of the elderly with polypharmacy was 78 years; this group is older than the average of the whole group. Apart from the fact that the group aged between 75 and 84 years outnumbers, in percentage terms, the entire research group, this cohort does not differ from the total group of elderly patients regarding its composition (Table 1). In the last 3 months of the study, the elderly in the research group used an average of 3.6 drugs (SD 3), 1.7 (SD 1.8) of these being used long-term. The polypharmacy is mainly minor: 69% of the group of elderly patients with polypharmacy use 2–3 drugs long-term simultaneously (28% of the whole population) (Table 2).

In the course of the 4 years, the mean number of drugs increased from 2.6 in the second quarter of 1994 to 3.6 in the last quarter of 1997; the long-term use increased in that period from an average of 1.3 (SD 1.6) drugs to 1.7 (SD 1.8).

The rate of increase of long-term drug use was about the same in both the minor and moderate polypharmacy categories, i.e. 40–48% (Fig. 1). In the major polypharmacy category, the percentage rate of increase was higher, i.e. 56%. In this respect, it should be noted that major polypharmacy also concerns the use of extremely large numbers of drugs (i.e. >8–10).

In Table 3, a comparison is made between the long-term drug use in 1997 and 1994. Long-term drug use remained stable in 817 patients (53%); 478 patients showing no long-term drug use, 138 patients taking only one drug long-term and 201 patients with stable use of two or more long-terms drugs, i.e. polypharmacy. The percentage of stable users decreased with the level of polypharmacy in 1994, being the smallest in the major polypharmacy category. Increase in long-term drug use occurred in 563 patients (36%), 400 (26%) of whom

TABLE 1 *Cohort of total elderly patients in 1994–1997* (n = *1544) and those with polypharmacy* (n = *634)*

Cohort	n = 1544	n = 634
Men	39%	35%
Mean age	73 years	78 years
65–74 years	62%	53%
75–84 years	32%	40%
⩾85 years	6%	7%

TABLE 2 *Elderly patients with polypharmacy in 1997* (n = *634) (percentages of the total cohort)*

Long-term drug use	No. of patients (n = 634)
2–3 drugs	438 (28%)
4–5 drugs	138 (9%)
>5 drugs	58 (4%)

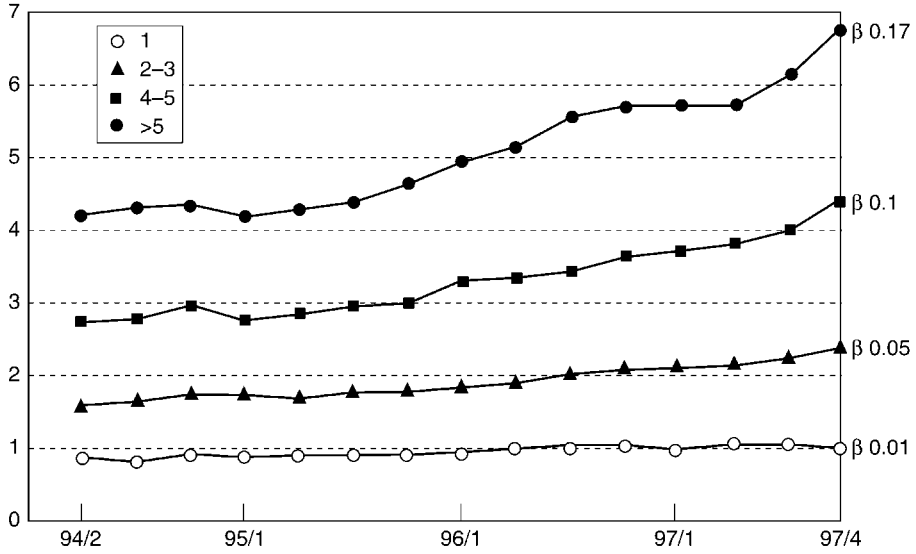

FIGURE 1 *Number of long-term drugs*

TABLE 3 *Long-term drug use in 1997 compared with 1994 (95% CI in parentheses)*

1994 1997	No long-term drugs (n = 776)	1 drug (n = 360)	2–3 drugs (n = 301)	4–5 drugs (n = 83)	>5 drugs (n = 24)	Total (n = 1544)
No long-term drugs	**85% (82–88) (n = 478)**	11% (9–14) (n = 64)	3% (2–5) (n = 18)	0% (0–1) (n = 2)	0% (0–1) (n = 2)	564
One drug	47% (42–52) (n = 163)	**40% (35–45) (n = 138)**	12% (8–15) (n = 41)	1% (0–3) (n = 4)	0% (0–1) (n = 0)	346
2–3 drugs	26% (23–40) (n = 116)	31% (27–36) (n = 136)	**37% (32–41) (n = 160)**	5% (3–8) (n = 22)	1% (0–2) (n = 4)	438
4–5 drugs	10% (10–17) (n = 14)	12% (8–19) (n = 17)	51% (42–60) (n = 70)	**22% (15–30) (n = 30)**	5% (2–11) (n = 7)	138
>5 drugs	8% (3–20) (n = 5)	8% (3–20) (n = 5)	22% (12–34) (n = 12)	43% (30–58) (n = 25)	**19% (10–32) (n = 11)**	**58**

were polypharmacy patients in 1997; 293 patients developed polypharmacy, as their long-term drug use increased from no drug or only one long-term drug in 1994 to two or more drugs in 1997. For 41 of these, the increase was large: from no drug or just one drug in 1994 to more than four drugs in 1997. For the other 252 patients, the increase was slow. For 164 (11%) patients, the long-term drug use decreased; 100 of them were polypharmacy patients in 1994.

In order to study the relationship between the increase of polypharmacy and health status and morbidity, the group showing an increase from no polypharmacy to polypharmacy (n = 293) was compared with the group which continued to use one or more drugs in that period (n = 341) and with the group which continued to use no drug or just one drug (n = 843) (Table 4).

The average number of diseases increased most in the group of elderly patients who showed the greatest increase in long-term drug use. However, the average number of disease episodes in those elderly patients who showed an increase in drug use (1.6) does not differ significantly from those of the two groups whose drug use stayed the same (1.4 and 1.7, respectively). In the small group with the greatest increase in drugs, the proportion of house calls in the total number of face-to-face contacts increased less than among those who showed a stable or slow increase in long-term drug use. The group that showed an increase in long-term drug use already had an important proportion of house calls in the total of all contacts (39%). The increase was small compared with the elderly with a small increase in long-term drug use, or those who mainly stayed stable.

In particular, the incidence of hypertension and atrial fibrillation is associated with an increase in polypharmacy [odds ratio (OR) 37.3 (95% CI 5.1–276) and 19.6 (95% CI 2.6–149), respectively]; the development of coronary ischaemia and psychotic complaints (mainly dementia) is associated to a lesser degree with the development of polypharmacy [OR 2.45 (95% CI 1.2–5.0) and 2.0 (95% CI 0.7–5.5), respectively] (Table 5). In the

TABLE 4 *Mean differences in average number of diseases (care episodes), average number of contacts with the GP and percentage of house calls in 1994 and 1997 in the elderly with and without an increase in long-term drug use (house calls as a percentage of total number of contacts with GP)*

	Without increase No polypharmacy (n = 843)	With polypharmacy (n = 341)	With increase Total group (n = 293)	Slow increase (n = 252)	Large increase (n = 41)
Mean difference in episodes	1.4	1.7	1.6	1.4	2.7
Mean difference in contacts	0.7	0.5	0.2	0.1	0.9
Mean difference in % house calls	7.5%	11.8%	8.5%	8.9%	5.3%

TABLE 5 *Incidence of diseases in the 4 years 1994–1997 in elderly patients with and without an increase in long-term drug use (as a percentage with 95% CI)*

	Without increase No polypharmacy (n = 843)	With polypharmacy (n = 341)[a]	With increase Total group (n = 293)[b]	Slow increase (n = 252)	Large increase (n = 41)
Diabetes	2.3 (1.4–3.5)	5 (2.9–7.9)	4.7 (2.6–7.9)	4.4 (2.2–7.7)	7.3 (1.5–20)
Coronary ischaemic disease	2.8 (1.8–4.2)	3.5 (1.6–5.5)	**8.2 (5.3–12)**	7.5 (4.6–11.5)	12.2 (4–26)
Congestive heart failure	1.9 (1.1–3.1)	5.6 (3.4–8.6)	5.8 (3.4–9.1)	6.0 (3.4–9.6)	9.8 (2.7–23)
Atrial fibrillation	1.4 (0.7–2.5)	0.3 (0–1.6)	**5.5 (3.2–8.7)**	5.5 (3–9.2)	5 (0.6–16.5)
Hypertension	5.2 (3.8–6.9)	0.3 (0–1.6)	**9.8 (6.7–13.9)**	9.5 (6.2–13.8)	14.7 (5.6–29)
Asthma/COPD	2.2 (1.4–3.5)	6.7 (4.3–9.6)	6.4 (4–9.9)	6.3 (3.7–10.1)	7.3 (1.5–20)
Osteoarthritis	0.9 (0.4–1.9)	0.8 (0.2–2.6)	1.3 (0.4–3.5)	1.3 (0.3–3.4)	2.4 (0–13)
Dementia	0.9 (0.4–1.9)	1.7 (0.7–3.8)	3.4 (1.7–6.2)	2.8 (1.1–5.6)	7.3 (1.5–20)
Diseases of oesophagus and stomach	1.8 (1.0–2.9)	1.8 (0.7–3.8)	1.7 (0.6–3.8)	1.6 (0.4–4)	2.4 (0–13)
Depression	0.6 (0.2–1.4)	0.9 (0.2–2.6)	2.4 (1–4.9)	2.4 (0.9–5.1)	2.4 (0–13)
Drug use without indication	0.5 (0.1–1.2)	–1.7 (0.7–3.7)	–0.6 (0.08–2.5)	–2.9 (1.1–5.6)	12.2 (4–26)

[a] Elderly patients with polypharmacy for the whole period; [b] elderly patients who developed polypharmacy

elderly group showing the greatest increase (n = 41), the incidence of hypertension, coronary ischaemic complaints and heart failure is higher than in the so-called slow increasers [OR 1.6 (95% CI 0.6–4.3), 1.7 (95% CI 0.6–4.9) and 1.7 (95% CI 0.5–5.4), respectively]. Asthma/COPD and diabetes also increase in this group with major polypharmacy, although to a lesser degree. Moreover, in this group of 'strong increasers', the incidence of drug use without a clear indication is strikingly high. Still more striking is the fact that the incidence of drug use without a clear indication decreases in the group of 'slow increasers'. The differences are, however, not significant compared with the group who show a slower increase in long-term drug use. The confidence intervals of the incidences in this group are large because of the relatively small number of 'strong increasers'.

The multiple regression analysis shows that besides age and the number of long-term drugs at the start of the study, the presence of hypertension, coronary ischaemic diseases, diabetes, atrial fibrillation, heart failure, or stomach disorders, and the use of drugs without a clear indication have a positive predictive value with regard to the number of long-term drugs at the end of the period (P <0.05). In particular, the number of long-term drugs that are used at the start of the study is the most reliable predictor (Table 6).

Discussion

The development of chronic polypharmacy is a slow process. In a period of 4 years, only 19% of the elderly changed from no or one drug to two or more drugs used long-term. In this period, the average long-term use increased from 1.3 to 1.7 drugs per person. This 31% increase is within the range of drug increases found in other longitudinal studies which show outcomes varying between 7 and 68%.[1–5,14]

TABLE 6 *Number of drugs, sex, age and existing morbidity as risk factors for development of polypharmacy at the end of the study period*

	P-value	Standardized regression coefficient β
No. of drugs at the start	0.0001*	0.45
Age	0.0002*	0.07
Sex	0.43	0.015
Diabetes	0.0001*	0.12
Coronary ischaemic diseases	0.0001*	0.13
Heart failure	0.01*	0.05
Hypertension	0.0001*	0.14
Asthma/COPD	0.12	0.03
Osteoarthritis	0.18	0.03
Atrial fibrillation	0.0013*	0.06
Dementia	0.59	-0.01
Diseases of oesophagus and stomach	0.03*	0.04
Depression	0.25	–0.02
Drug use without an indication	0.03*	0.06

The different results of the various studies can be explained by the variations in duration of drug use and the duration of the research period. Our study focuses on long-term drug use and covers a research period of 4 years. The few studies done on the development of drug use examined all drugs used, and the research periods varied from 4 to 10 years. Moreover, the method of collecting data (mainly by interview) as well as the representativeness of the study population account for the differences found.

For example, Stewart and colleagues examined prescribing practices in a retirement community in the USA over a 10-year period, but acknowledged that their study sample was highly selected and unrepresentative; all participants had to be healthy enough to attend and participate in the study.[4] In a longitudinal study in Sweden, all participants were 70 years of age at the start of the study and not representative of the Swedish elderly population.[14] Our patient population of the three general practices is comparable with those in other practices in the north of The Netherlands.[15] Nevertheless in our study too, selection bias is inevitable, because elderly patients who died, those who left the practices or those who were new to the practice during the study period have been excluded from the study. This involved a total of 653 elderly patients. On these grounds, one must assume that the cohort of the study is healthier than a random group of elderly subjects.

Polypharmacy develops slowly. A large increase is found in barely 3% of the group of elderly patients (n = 41) showing an increase in long-term drug use of from none or just one drug to four or more drugs. These findings correspond to the results from the study of Heerdink *et al*. They reported that it took people who did not use any long-term drug at all ~4 years to change over to one long-term drug.[5]

Besides the increase in diseases and worsening of diseases, the literature also mentions other factors as being responsible for the increase in polypharmacy, i.e. ageing, moving to a residential or nursing home and hospitalization.[6,7] The patient's expectations, the GP's attitude and consultations with several doctors have been associated with an increase in multiple drug use.[16,17] Our study focuses mainly on increases in diseases and, in particular, a few chronic diseases.

The development of polypharmacy is not related to the increase in the number of diseases. This implies that polypharmacy may also develop in cases of just one disease, e.g. when deterioration of the health status sets in. The increase in the proportion of house calls—as a possible measurement of health status—in the group of elderly patients with the strongest increase in drugs and disease episodes is smaller, however, than in the group who show a slight increase or who stay mainly stable in terms of drug use. The proportion of house calls in this group of elderly patients was already quite notable at the start of the period; their health status obviously was already a reason for more house calls. In earlier studies, an increase in contact frequency was found among the elderly when their health was deteriorating and their co-morbidity increasing.[18] The outcome of this study makes doubtful the assumption that an increasing percentage of house calls in relation to the total number of contacts indicates a deterioration of the health status. There are obviously other factors causing a deterioration of the health status, which were not assessed in this study.

Increasing polypharmacy in the elderly is mainly concomitant with the occurrence of atrial fibrillation, hypertension and, to a lesser degree, coronary ischaemia and dementia. Heart failure and use of medication without a clear indication play a part in the group of elderly patients who show a large increase in their drug use. However, the number of patients in this group was small (n = 41), so no absolute conclusions can be drawn regarding the increase in polypharmacy. Because of the small numbers in this study, we were not able to draw any valuable conclusions with respect to diseases such as dementia and depression.

The number of long-term drugs which a patient already uses is the best predictor of polypharmacy at the end of the study period. This is in agreement with the findings of other studies.[5,19] In particular, elderly patients who use more than four long-term drugs simultaneously are more likely to add yet another drug in a short time than those who use fewer than four long-term drugs.[5] The latter group took an average of a year and a half before a new long-term drug was added. Relevant morbidity-related predictors of polypharmacy in the long-term are the occurrence of diabetes, coronary ischaemic heart diseases and hypertension. Also the use of drugs without a clear indication is concomitant with an increased risk of (more) polypharmacy in the future. It is remarkable that a large increase of polypharmacy is associated with more use of drugs without a clear indication, while, on the other hand, in the case of a slightly increasing or stable polypharmacy use even decreases over the 4-year period. In our case, this group comprises only a few elderly patients <41, some of whom may be considered responsible for this large increase. Earlier studies proved that the indications for sedatives/hypnotics, laxatives and analgesics in particular were ambiguous.[9] This presumably thus concerns a small group of elderly patients who make a strong appeal to the physician to prescribe medication, or who, in spite of the physician's explicit advice, are not inclined to stop taking these drugs.

In our study, the long-term drug use, i.e. longer than two-thirds of the research period, has been examined, resulting in a relatively small group of elderly people with moderate or major polypharmacy. Because the deceased elderly patients were excluded in order to be able to have a complete data set over the the entire period, the results in this study apply to relatively healthy people. This selection bias may cause under-reporting.

In the light of our results, it is clear that the possibility of reducing polypharmacy should not be overrated. The diseases most significant for developing polypharmacy usually need complex drug regimens. The best option to realize reduction lies in examining the drugs used without a clear indication, as this happens frequently in practices, particularly with regard to psychotropic drugs. Over the years, many approaches have been tried to tackle this particular issue, with varying degrees of success.[20–23]

From the point of view of medication control and high risk groups, surveillance and attendance to the elderly suffering from cardiovascular diseases is of great importance for the prescribing physician.

References

[1] Stewart RB, Moore MT, May FE, Marks RG, Hale WE. A longitudinal evaluation of drug use in an ambulatory elderly population. *J Clin Epidemiol* 1991; **44:** 1353–1359.

[2] Rumble RH, Morgan K. Longitudinal trends in prescribing for elderly patients: two surveys four years apart. *Br J Gen Pract* 1994; **44:** 571–575.

[3] Jylha M. Ten-year change in the use of medical drugs among the elderly. A longitudinal study and cohort comparison. *J Clin Epidemiol* 1994; **47:** 69–79.

[4] Stewart RB, Moore MT, May FE, Marks RG, Hale WE. Changing patterns of therapeutic agents in the elderly: a ten year overview. *Age Ageing* 1991; **20:** 182–188.

[5] Heerdink ER. Clustering of drug use in the elderly: population-based studies into prevalence and outcomes. Thesis, University of Utrecht, 1995.

[6] Hale WE, May FE, Marks RG, Stewart RB. Drug use in an ambulatory elderly population: a five-year update. *Drug Intell Clin Pharm* 1987; **21:** 530–535.

[7] Simons LA, Tett S, Simons J *et al*. Multiple medication use in the elderly. Use of prescription and non-prescription drugs in an Australian community setting. *Med J Aust* 1992; **157:** 242–246.

[8] Bjerrum L, Rosholm JU, Hallas J, Kragstrup J. Methods for estimating the occurrence of polypharmacy by means of a prescription database. *Eur J Clin Pharmacol* 1997; **53:** 7–11.

[9] Bange R, Brandwijk K. Geneesmiddelen bij ouderen: mag het ook iets minder zijn? *Huisarts Wet* 1990; **33:** 426–428.

[10] Veehof LJG, Stewart R, Meyboom-de Jong B, Haaijer-Ruskamp FM. *Polyfarmacie in de huisartspraktijk*. Een verkenning.1996 NCG. Groningen.

[11] Lamberts H, Wood M (eds). *ICPC, International Classification of Primary Care*. Oxford: Oxford University Press, 1987.

[12] WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC Classification and DDD Assignment*. Oslo: WHO, 1996.

[13] Veltman MTM. Huisartsgeneeskundige zorgepisoden: analyse van een zevenjaarsbestand. Thesis, University of Amsterdam, Meditekst, 1995.

[14] Landahl S. Drug treatment in 70–82 year old persons. *Acta Med Scand* 1987; **221:** 179–184.

[15] Van der Werf GTH, Smith RJA, Stewart RE, Meyboom-de Jong B. *Spiegel op de huisarts; over registratie van ziekte, medicatie en verwijzingen in de geautomatiseerde huisartspraktijk*. Rijksuniversiteit Groningen, 1998.

[16] Sharpe TR, Smith MC, Barbre AR. Medicine use among the rural elderly. *J Health Soc Behav* 1985; **26:** 113–127.

[17] Williams P, Rush DR. Geriatric polypharmacy. *Hosp Pract* 1986; **21:** 109–120.

[18] Buis J. Thirteen chronic diseases, in particular stroke. A survey of the elderly. Thesis, Groningen, 1998.

[19] Fillenbaum GG, Horner RD, Hanlon JT, Landerman LR, Dawson DV, Cohen HJ. Factors predicting change in prescription and nonprescription drug use in a community-residing black and white population. *J Clin Epidemiol* 1996; **49:** 587–593.

[20] Vissers FJHA, Knottnerus JA, Van der Grinten RF, Van der Horst FGEM. Interventies in de eerste lijn bij langdurig gebruik van benzodiazepinen. Een literatuurstudie. *Huisarts Wet* 1997; **40:** 244–247.

[21] Salinsky JV, Dore CJ. Characteristics of long-term benzodiazepine users in general practice. *J R Coll Gen Pract* 1987; **37:** 202–204.

[22] Holm M. One year follow up of users of benzodiazepines in general practice. *Dan Med Bull* 1990; **37:** 188–191.

[23] Packham C. Patients who have discontinued long-term benzodiazepine treatment. *Br J Gen Pract* 1992; **42:** 130.