

Analysis of polypharmacy in older patients in primary care using a multidisciplinary expert panel

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ABSTRACT

Background

Many older patients suffer from chronic diseases for which medicines should be used. Because of the higher number of medicines used and decline in hepatic and renal function, older patients are more prone to problems caused by these medicines. Therefore, it is important to review pharmacotherapy concerning older patients in primary care in a reliable way.

Aim

To determine the nature, volume and clinical relevance of prescription-related points of attention in the elderly.

Design of study

Analysis of pharmacotherapy by a multidisciplinary expert panel consisting of GPs, geriatric specialists, clinical pharmacists and community pharmacists.

Setting

Pharmacotherapy of 102 home-dwelling older patients on polypharmacy (≥ 75 years, using ≥ 4 medicines continually) living in the Netherlands.

Method

The analysis of medication-profiles was based on a two-round consensus method.

Results

When performing medication reviews for older people it seemed that for almost all (98%) improvement in pharmacotherapy could be made. For 94% of all patients points of attention could be identified in prescribed medicines, of which 30% was considered to be of direct clinical relevance. In 61% of all patients a medicine could be added to improve pharmacotherapy, 25% of these prescribing omissions were considered to be of direct clinical relevance.

Conclusion

The regular performance of medication reviews should be part of routine in primary care as it yields significant numbers of prescription-related points of attention. Although they were not all considered to be of direct clinical relevance, all points of attention do ask for a signal to the prescribing physician. This paper is not implying poor practice or poor reviewing practice but documenting the need for performing regular medication reviews.

Keywords

elderly; inappropriate prescribing; medication reviews; pharmaceutical care.

INTRODUCTION

In the Netherlands 14% of the population consists of older people (≥ 65 years old). This proportion of the population is responsible for as much as 39% of all expenses on medicines as delivered by community pharmacies. People aged 65 years or over use three times as many medicines as compared to the whole population in the Netherlands (three medicines daily on average). People of 75 years or over use on average as many as four medicines daily.¹ Older people use many medicines because they suffer from more chronic conditions that need treatment by means of pharmacotherapy. However, older people are more prone to adverse drug reactions, resulting from age-related factors such as changes in drug distribution, metabolism and excretion, and in receptor sensitivity as well as from drug–drug interactions and drug–disease interactions caused by prescribing of multiple drugs.^{2–5} In other words, prescribing in older patients involves balancing conflicting demands, and the benefit:risk ratio should be considered when deciding whether to initiate pharmacotherapy.

Although it is not possible to prevent all prescription-related problems in older people, several studies have shown that it is possible to

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Submitted: 20 May 2005; Editor's response: 5 August 2005; final acceptance: 25 January 2006.

©British Journal of General Practice 2006; 56: 504–510.

reduce the occurrence of prescription-related problems by means of a medication review.⁶⁻⁹ In such a medication review, complete pharmacotherapy of an individual patient is assessed by a trained professional (GP and/or pharmacist). In the UK regular medication reviews for older people on long-term medication were recommended by the Department of Health to maximise therapeutic benefit and minimise potential harm,¹⁰ and this practice has been included in the Community Pharmacy Contractual Framework for all patients on long-term medication in the UK.¹¹

In this article we describe the occurrence and clinical relevance of prescription-related points of attention found in older patients when use is made of an in depth and comprehensive approach with medication reviews performed by both prescribers and pharmacists. The occurrence of user-related pharmaceutical care problems in the same group of older patients had been determined in a previous study,¹² creating insight in to whether it appears more effective to focus quality improvement interventions on prescribers (in particular GPs), or on the users of medicines.

This study is the first in-depth analysis by a large expert panel and focuses on a wider and more comprehensive set of prescription-related points of attention than previous studies have done.¹³⁻²¹ It therefore provides a more complete and accurate picture of the size and types of prescription-related points of attention faced by older patients as well as the clinical relevance of them. Whether or not precautions were taken by the prescribing physician (such as regularly checking potassium levels) to prevent these potential problems is not included in this study. However, the results of this study should give some insight in to the process of medication review that can be used for setting up better and more reliable medication reviews in the future.

METHOD

Study design and population

An analysis was performed of pharmacotherapy of 107 older people living in the community in the southeast of the Netherlands. Pharmacy dispensing

data were collected from November 2001 to December 2002. The assessment of pharmacotherapy by the expert panel was based on a consensus method.

Patients were selected from the participants of a study on user-related problems¹² with 298 home-dwelling participants of ≥ 75 years old who were being prescribed four or more medicines chronically, and were living in the south of the Netherlands. In the previous study, nine pharmacies were included (convenience sample). These pharmacies each contacted one to three GPs. The pharmacists and GPs invited eligible patients to participate in the study: patients were included if they returned the application form, including their informed consent.

For each GP participating in this study ($n = 18$), six patients were picked at random, resulting in a total of 107 patients (for one GP only five eligible patients could be pointed obtained).

Variables and instruments

Types of prescription-related points of attention. Inappropriate prescribing was assessed based on the aspects described in Table 1.

Clinical relevance of prescription-related points of attention. Panel members rated the clinical

Table 1. Aspects of inappropriate prescribing including examples for each aspect.

Example	Description of the problem
1. Medicine not useful (no indication, no proven effectiveness or better/safer alternatives available)	Prescribing clofibrate, for which much safer and more effective alternatives exists
2. Medicine inappropriate for use in older patients	Prescribing diazepam, which has a long half-life time
3. Prolonged prescribing of hypnotics	Medicine is not taken for a correct duration
4. Dosage exceeds the suitable dosage for older patients	Prescribing flurazepam in a dosage exceeding 15 mg daily
5. Unnecessary therapeutic duplication	Prescribing cyclobarbitol and a benzodiazepine
6. Contraindication known (drug-disease interaction)	Prescribing indometacin to a patient suffering from heart failure
7. Medicine used for treatment of a side-effect caused by another medicine	Omeprazole for treatment of stomach problems probably caused by ketoprofen (NSAID)
8. Interaction with another medicine (drug-drug interaction)	Prescribing cotrimoxazol to a patient using acenocoumarol (coumarin-derivative) that causes problems in managing INR
9. Omission of drug therapy that is indicated for the treatment or prevention of a condition	Lack of prescribing a laxative to a patient
10. Medicine used in/provided by unsuitable administration aids for older people	Prescribing different types of inhalation devices to one patient

How this fits in

Older people are more prone to adverse drug reactions, but they also use a higher number of medicines. Improvement in pharmacotherapy for almost all older patients can be made.

Table 2. Levels of clinical relevance for prescription related pharmaceutical care problems, including examples for each score of clinical relevance.

Score, description	Example
0, Aspect is not applicable	–
1, Aspect is applicable, but not clinically relevant	Use of vitamin C preparations without an indication known
2, Aspect is applicable and potentially clinically relevant; extra information is needed to determine the relevancy of these points of attention (such as blood pressure, other measurements or clinical condition of the patient)	Drug–drug interaction between digoxin and diuretics; when potassium levels are regularly checked this interaction will not cause any problems
3, Aspect is applicable and clinically relevant; these aspects are of clinical relevance in all instances	Prescribing glibenclamid, which is not suitable for use in older patients because it can cause prolonged hypoglycaemia

relevance of points of attention and prescribing omissions by means of a score from zero to three. Points of attention were considered as having clinical relevance if they could lead to a deterioration in general health status of the patient (see Table 2).

Procedures

Expert panel. The expert panel consisted of two GPs, two community pharmacists, two older-patient specialised internal medical specialists and two clinical pharmacists. Panel members were selected on the basis of their nationally recognised expertise in pharmacology and/or clinical older patient pharmacology.

Individual scoring. For each of the 107 participating older patients the panel members received a pharmacy record, a graphic medication record, the reasons for prescribing the medicines (provided by the GP), and a scoring form, containing all medicines regularly taken as determined by pharmacy records and the previously named aspects (see Table 1).¹⁰ The scoring forms were completed and sent back to the researcher by individual panel members. Before the consensus meetings, panel members received overviews in which their own scores were reflected in the light of the scores of the other panel members.

Consensus meeting. During the consensus meetings aspects of medicines were discussed that indicated a lack of consensus or were of clinical relevance. The researcher (a pharmacist) selected the points of attention that needed further discussion, including all items that had a score of at least six (when taking scores of all experts together) and all items that had scored at least a single three (clinically relevant item). An independent

chairperson led the meeting. Panel members were invited to raise any additional topic that they considered of concern.

In case panel members were not able to join the meeting the researcher held an individual interview with the panel members to discuss his/her scores, and brought it into the discussion during the group meetings.

After the panel meeting, reports of the meeting, made by the researcher, were sent by email to all panel members, so that they could give their comments. Issues that remained unclear and comments of panel members were discussed again during the next consensus meeting, until consensus was reached.

Data analysis. After the panel discussions the scored points of attention (consensus) were analysed with SPSS 11 (SPSS Inc. Chicago, Illinois, US), and an inventory of all prescription-related points of attention was made. During the panel discussions it seemed that a score of 1 was not always used consequently; when an aspect was not relevant it was not scored at all. Therefore, in the results, only points of attention with a score of 2 (potential clinical relevant) or 3 (clinically relevant) are included.

RESULTS

Consensus meetings

In total, five panel discussions (four on telephone and one in person) took place during which the medications of 107 patients were discussed. On average, there were more than six panel members present during the panel discussions (one time, all experts were present, one time only five experts were able to participate, for two discussions six panel members participated and in one instance seven panel members were present).

On average, the total panel consensus contained more (and other) points of attention than the individual scoring lists. It appeared that each panel member had his/her own area of expertise. The individual written score κ value showed a variation for each item and each panel member (range 0.01–0.88). The average κ -value after the round in writing for all items and all panel members was 0.34 (slight agreement). The discussion sometimes yielded additional points of attention because of the interaction between panel members of different professions. During the consensus meetings, however, consensus was reached for all items.

Patients

In the panel discussion the medications of 107 elderly patients were discussed. After an evaluation

of medicine use, five older patients were excluded because they used fewer than four medicines. The included patients were on average 81 years of age, were almost two-thirds female (62%), and used on average 6.8 medicines chronically. Forty-one per cent of the included patients got their prescriptions only from one physician.

In total, 102 older patients used 755 medicines. Medicines for cardiovascular diseases were prescribed most frequently (36% of the total number of medicines used), followed by medicines for the central nervous system (13%), the alimentary tract and metabolism (12%), and blood and blood-forming organs (10%).

In the medication records of 98% of all patients, points of attention were identified. In 4% of these medication profiles the expert panel had no comments on the medicines currently used, but one or more medicines could possibly or should be added to improve pharmacotherapy.

Number, type and clinical relevance of prescription-related points of attention

Panel members rated 457 points of attention considering prescribed medicines used by 96 older patients. Thirty per cent of these recommendations were considered to be of direct clinical relevance, the remaining 70% was considered to be of potential clinical relevance. The latter category of problems can possibly partly be solved by reviewing the medical records (such as measures of potassium or blood pressure), but whether or not these measures were regularly performed by the GP was not registered in our study.

Table 3 shows the distribution of the points of attention by various problem categories.

Medicines considered as being not useful are reported most frequently, seen in anatomical therapeutic classification (ATC) group N (medicines for the nervous system, 21%) and C (medicines for the cardiovascular system, 20%). The problem category seen second most frequently is prescribing medicines for an incorrect period of time, almost exclusively (88%) seen in ATC group N, and prescribing medicines in a dose not appropriate for older people, seen in group C (56%) and N (40%). Drug–drug interactions are also reported frequently, drug–drug interactions are mainly (57%) caused by medicines from ATC group C, medicines for the cardiovascular system.

Table 4 shows the percentages of medicines out of main ATC groups having at least one prescription-related point of attention of potential clinical relevance. The main ATC group R (medicines for the respiratory system) is the group with the highest number (relatively); this is mainly

Table 3. Number and types of prescription-related points of attention (including points of attention with potential clinical relevance and points of attention with direct clinical relevance).

Type of prescription-related point of attention	Number of prescription-related points of attention (% of total number of prescription-related points of attention)
Medicine not useful (no indication, no proven effectiveness or better alternatives available)	76 (19)
Dose not appropriate for >75 years	57 (14)
Incorrect period	57 (14)
Medicine interaction	55 (13)
Medicine inappropriate for >75 years	51 (13)
Inappropriate administration form or aids	48 (12)
Medicine used for treatment of side effects of another medicine	27 (7)
Contraindication known	19 (5)
Unnecessary therapeutic duplication	18 (4)
Total	408 (100)

caused by concerns of panel members about the suitability of the inhalation devices for elderly patients, but also about the use of mucolytics. There is some doubt whether these preparations are effective. At the time of our study, the leading Dutch Drug Compendium (Farmacotherapeutisch Kompas) discouraged the use of oral mucolytics, this discouragement is still present in the 2006 edition.²² The panel felt that their use should, at the very least, be carefully considered.

Main ATC group M (medicines for the musculoskeletal system) is the group with the second highest number of points of attention, mainly caused by drug–drug interactions caused by NSAIDs (26%), use of hydroquinine or NSAIDs being less appropriate for the elderly (26%), and use of NSAIDs when other analgesics are indicated (18%).

In the main ATC group G (medicines for the genitourinary system and sex hormones) recommendations were related to medicines for incontinence with a marginally proven effectiveness (while leading to side effects) for which alternatives exist causing fewer side effects (42%) and inappropriateness for older people because of anticholinergic side-effects (33%). In group N (medicines for the nervous system) points of attention were mainly related to prolonged prescribing of benzodiazepines (50%). Points of attention in this group were aimed at prescribing long-acting benzodiazepines that are less suitable for use in the elderly (27%) and prescribing drugs — mainly benzodiazepines — in dosages exceeding the geriatric daily dose (23%).

In some ATC groups, high percentages of prescriptions have at least one recommendation.

Table 4. Number of recipes within a main anatomical therapeutic classification (ATC) group.^a

Main ATC group	Number of recipes with at least one prescription-related point of attention (% in main ATC group)	Total number of recipes in main ATC group	Type of prescription related point of attention seen most within the particular main ATC group (percentage in main ATC group)
A. Alimentary tract and metabolism	30 (32.3)	93	Medicine for treatment side effect of other medicine (20.5) Medicine not useful (8.7)
B. Blood and blood forming organs	19 (24.4)	78	Medicine not useful (15.4) Drug–drug interaction (8.9)
C. Cardiovascular system	97 (35.7)	272	Drug–drug interaction (18.0) Dose not correct for >75 years (11.8)
G. Genitourinary system and sex hormones	8 (66.7)	12	Medicine not useful (41.6) Medicine not suitable for >75 years (33.3)
H. Systemical hormonal preparations (excluding sex hormones and insulin)	6 (31.6)	19	Unnecessary therapeutic duplication (15.8) Medicine not useful (10.6)
J. Anti-infectives for systemic use	3 (42.9)	7	Length of prescription (28.6) Drug–drug interaction (14.3)
M. Musculoskeletal system	28 (73.7)	38	Drug–drug interaction (26.4) Medicine not suitable for >75 years (26.3)
N. Central nervous system	65 (65.0)	100	Length of prescription (50.0) Medicine not suitable for >75 years (27.0)
R. Respiratory system	58 (90.6)	64	Administration form not suitable for >75 years (73.4) Medicine not useful (20.4)
S. Sensory organs	4 (9.5)	42	Medicine for treatment side effect of other medicine (4.8) Length of prescription (4.8)

^aWith at least one point of attention (including points of attention with potential clinical relevance and points of attention with direct clinical relevance), total number of recipes in main ATC group and a description of the type of points of attention seen most (percentage of all points of attention in the main ATC group).

These recommendations can be categorised into specific groups of points of attention, more than half of all points of attention can be identified by looking at these specific medicines or groups of medicines.

Prescribing omissions

By reviewing the complete medication profiles, it appeared that 101 medicines might have been needed to improve the quality of medication therapy in 62 patients (61% of all older patients). Score 2 (a medicine might be added to improve pharmacotherapy depending on the general condition of the patient) was scored in 76% of all cases and seen in 52% of all older patients. Twenty-five per cent of the omitted medicines had a score of 3, meaning that according to prescription guidelines a medicine should be added to improve pharmacotherapy. These prescribing omissions were seen in 23% of all elderly patients.

More than half of all prescribing omissions (60%) were found in main ATC group C (medicines for the cardiovascular system), for example, the need of adding an ACE-inhibitor to pharmacotherapy of an elderly patient with heart failure. Twenty-two per cent of the prescribing omissions could be

categorised in main ATC group B (blood and blood forming organs), such as adding a thrombocyte-aggregation-inhibitor to the pharmacotherapy of an older patient with angina pectoris. Ten per cent of all omitted medicines belonged to main ATC group R (respiratory system); a medicine should probably be added to optimise ATCMA/COPD treatment, such as rescue-medication (short-acting β_2 -sympathomimetics) for the treatment of a patient only using long-acting β_2 -sympathomimetics.

DISCUSSION

Summary of main findings

In this study, prescription-related points of attention of potential clinical relevance were found in pharmacotherapy of almost all included patients. One-third of the points of attention found in prescribed medicines were considered to be of direct clinical relevance, implying that these prescriptions should be changed unconditionally. The remaining two-thirds were potentially relevant, meaning that adjustment would depend on clinical measurements or specific clinical parameters of the patient, whether or not these precautions were taken by the physician was not registered in our study. In addition, the panel determined that a

relevant medication was missing or potentially missing in almost two-thirds of the patients.

Strengths and the limitations of the study

This study is the first in-depth analysis by a large expert panel and focuses on a wide and comprehensive set of prescription-related points of attention. It provides a complete and accurate picture of the number and types of prescription-related points of attention faced by older patients as well as the clinical relevance of these problems.

Our study is not without limitations. First, the patients in our study consisted of a limited sample. Although their number was quite high for such a comprehensive method of evaluation, some types of prescribing problems — in particular those that occur rarely — may be underrepresented. Second, consensus approaches always entail a risk that some panel members are more influential than others. Third, our expert panel has identified points of attention on the basis of a medication record and the indications for the medicines as given by the physician. Our panel had no medical records at their disposal. In most instances, regular checks and measurements will be performed by the physician and in some instances a second choice medicine will be optimal treatment because other medicines will not be tolerated by the particular patient. Our study does indicate a high number of points of attention in daily practice. However, a part of these points of attention will be dealt with already by means of regular checks. This paper is not implying poor practice or poor reviewing practice but documenting the need for regular medication reviews.

Comparison with existing literature

Recommendations were mainly seen in the medicines for the respiratory system, the cardiovascular system and the nervous system. Points of attention regarding medicines for the cardiovascular system were mainly caused by drug–drug interactions, which were in most instances not of direct clinical relevance. In daily practice, high numbers of drug–drug interactions are seen within this group, and many problems caused by these interactions will be prevented by regularly measurements (such as potassium levels or blood pressure).^{23–24}

Recommendations regarding medicines for the respiratory tract were mainly aimed at the suitability of inhalation devices used for older patients. This is consistent with other studies that also found that older patients frequently have problems taking inhaled medication,^{25,12} therefore such a signal to the physician may be relevant.

Most points of attention of direct clinical relevance were seen in the group of medicines for the central nervous system, which were in particular related to benzodiazepine use. Problems included the use for an incorrect period, in dosages exceeding the geriatric daily dosage and use of substances with a long half-life time that are not suitable for use in older patients. Prolonged use of hypnotics, particularly in the elderly, is a widespread problem, as numerous studies concerning inappropriate prescribing for the elderly have shown.^{13,14,20,26}

In almost two thirds of the patients, prescribing omissions were identified, of which one out of four were of direct clinical relevance. Prescribing omissions are only scarcely described in studies concerning inappropriate prescribing for the elderly,²⁷ in spite of studies that prove that a substantial number of older patients is not receiving omitted but necessary pharmacotherapy for established diagnosis.^{28–31} Prescribing omissions may place older patients at higher risk for preventable adverse consequences. Hence, medication reviews should point at the quality of complete medication profiles and not only at the quantity of drugs prescribed.

Implications for future research or clinical practice

Over half of detected points of attention recurred in only a handful of drug classes, suggesting that medication reviews of older outpatients on polypharmacy may benefit from a computerised screening tool. Although such a computerised screening tool could detect a large proportion of potential problems, the detection of various other problems in our analysis shows that such a tool should be supplemented with a more implicit method of assessment. The professional judgement of a complete medication profile by an experienced healthcare provider can detect problems that would go unnoticed if one would rely solely on computerised screening. The overall κ -value indicated slight agreement after the round in writing. All panel members seemed to have their own speciality. During the consensus meetings, however, consensus about all aspects was reached. In some instances panel members had to make out their case, in other instances consensus was reached quickly because other panel members realised they had overlooked a particular problem. Another interesting observation (data not shown) was that about 15% of the points of attention could only be detected because the panel was not only supplied with the medications prescribed but also with the reasons for prescribing them. Together

these findings raise the possibility that medication reviews ideally should be performed by more than one healthcare professional, ideally of different professions, with the medical record at their disposal. Further research is needed to confirm these assumptions.

All in all, we conclude that it appears advisable to perform medication reviews for home-dwelling older patients by GPs, community pharmacists and other specialists. It yields significant numbers of relevant prescription-related points of attention and a potential for quality improvement of prescriptions for older patients living in the community.

Funding body

This study was funded by a research grant from the Royal Association for the Advancement of Pharmacy (KNMP)

Ethics committee

Before the start of this study our study protocol was applied at the Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen (CMO-nr 2001/141) for ethical approval. This board decided that based on the study protocol and the WMO regulations (regulations for research including human) no ethical approval was needed

Competing interests

The authors have stated that there are none

Acknowledgements

The authors thank YA Hekster, PharmD, PhD; P van den Hombergh, MD, PhD; PAF Jansen, MD, PhD; JR van der Laan, MD; CPJM Lemmens, PharmD; CK Manneke, MD, PhD and EC Weening PharmD for their contribution to the expert panel. Furthermore, we want to thank the participating pharmacists and GPs for their contribution to our study.

REFERENCES

1. Tinke JL, Griens AMGF. Facts and Figures 2004. The Hague, The Netherlands: Foundation for Pharmaceutical Statistics, 2004. <http://www.sfk.nl> (accessed 1 Jun 2006).
2. Turnheim K. Drug therapy in the elderly. *Exp Gerontol* 2004; **39**(11-12): 1731-1738.
3. Denham MJ, Barnett NL. Drug therapy and the older person: role of the pharmacist. *Drug Saf* 1998; **19**(4): 243-250.
4. Jansen PAF. Valkuilen bij medicatie gebruik door ouderen [Pitfalls in medication use by the elderly]. *Geneesmiddelen bulletin* 2000; **34**(5): 53-59.
5. Beers MH, Ouslander JG. Risk factors in geriatric drug prescribing. A practical guide to avoiding problems. *Drugs* 1989; **37**(1): 105-112.
6. Zermansky AG, Petty DR, Raynor DK, et al. Randomised controlled trial of clinical medication review by a pharmacist of elderly patients receiving repeat prescriptions in general practice. *BMJ* 2001; **323**(7325): 1340-1343.
7. Kraska J, Cromarty JA, Arris F, et al. Pharmacist-led medication review in patients over 65: a randomized, controlled trial in primary care. *Age Ageing* 2001; **30**(3): 205-211.
8. De Smet PA, Dautzenberg M. Repeat prescribing: scale, problems and quality management in ambulatory care patients. *Drugs* 2004; **64**(16): 1779-1800.
9. Rollason V, Vogt N. Reduction of polypharmacy in the elderly: a systematic review of the role of the pharmacist. *Drugs Ageing* 2003; **20**(11): 817-832.
10. Department of Health. *National service framework for older people*. London: Department of Health, 2001. <http://www.dh.gov.uk/assetRoot/04/07/12/83/04071283.pdf> (accessed 2 Jun 2006).
11. Department of Health. *Medicines, pharmacy and industry. Community pharmacy contractual framework*. London: Department of Health, April 2005. <http://www.dh.gov.uk/PolicyAndGuidance/MedicinesPharmacyAndIndustry/fs/en> (accessed 2 Jun 2006).
12. Denneboom W, Dautzenberg MG, Grol R, Smet PA. User-related pharmaceutical care problems and factors affecting them: the importance of clinical relevance. *J Clin Pharm Ther* 2005; **30**(3): 215-223.
13. Hanlon JT, Schumacher KE, Boulton C, et al. Use of inappropriate prescription drugs by older people. *J Am Geriatr Soc* 2002; **50**(1): 26-34.
14. Pitkala KH, Strandberg TE, Tilvis RS. Inappropriate drug prescribing in home-dwelling, elderly patients: a population-based survey. *Arch Intern Med* 2002; **162**(15): 1707-1712.
15. Raji MA, Ostir GV, Markides KS, et al. Potentially inappropriate medication use by elderly Mexican Americans. *Ann Pharmacother* 2003; **37**(9): 1197-1202.
16. Goulding MR. Inappropriate medication prescribing for elderly ambulatory care patients. *Arch Intern Med* 2004; **164**(3): 305-312.
17. Willcox SM, Himmelstein DU, Woolhandler S. Inappropriate drug prescribing for the community-dwelling elderly. *JAMA* 1994; **272**(4): 292-296.
18. Zhan C, Sangl J, Bierman AS, et al. Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey. *JAMA* 2001; **286**(22): 2823-2829.
19. Stuck AE, Beers MH, Steiner A, et al. Inappropriate medication use in community-residing older persons. *Arch Intern Med* 1994; **154**(19): 2195-2200.
20. Howard M, Dolovich L, Kaczorowski J, et al. Prescribing of potentially inappropriate medications to elderly people. *Fam Pract* 2004; **21**(3): 244-247.
21. Schumacher K, Hanlon JT, Weinberger M, et al. Appropriateness of medication prescribing in ambulatory elderly patients. *J Am Geriatr Soc* 1994; **42**(12): 1241-1247.
22. The Health Insurance Board: drug compendium. Monograph on acetylcysteine. College voor zorgverzekeringen. <http://www.cvzkompassen.nl/fk> (accessed 8 Jun 2006).
23. Merlo J, Liedholm H, Lindblad U, et al. Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study. *BMJ* 2001; **323**(7310): 427-428.
24. Bergk V, Gasse C, Rothenbacher D, et al. Drug interactions in primary care: impact of a new algorithm on risk determination. *Clin Pharmacol Ther* 2004; **76**(1): 85-96.
25. Armitage JM, Williams SJ. Inhaler technique in the elderly. *Age Ageing* 1988; **17**(4): 275-278.
26. Mort JR, Aparasu RR. Prescribing potentially inappropriate psychotropic medications to the ambulatory elderly. *Arch Intern Med* 2000; **160**(18): 2825-2831.
27. Higashi T, Shekelle PG, Solomon DH, et al. The quality of pharmacologic care for vulnerable older patients. *Ann Intern Med* 2004; **140**(9): 714-720.
28. Barakat K, Wilkinson P, Deane A, et al. How should age affect management of acute myocardial infarction? A prospective cohort study. *Lancet* 1999; **353**(9157): 955-959.
29. Rochon PA, Gurwitz JH. Prescribing for seniors: neither too much nor too little. *JAMA* 1999; **282**(2): 113-115.
30. Lipton HL, Bero LA, Bird JA, McPhee SJ. Undermedication among geriatric outpatients: results of a randomized controlled trial. *Ann rev gerontol ger* 1992; **12**: 95-108.
31. Gollub SB. Is intensive drug therapy appropriate for older patients? *Lancet* 1999; **353**(9157): 940-941.