Information for rational drug prescribing to older patients

Erna Beers

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Availability and applicability

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Information for rational drug prescribing to older patients

Availability and applicability

Informatie voor het rationeel voorschrijven van geneesmiddelen aan oudere patiënten
Beschikbaarheid en toepasbaarheid
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op maandag 14 april 2014 des middags te 2.30 uur

door

Erna Beers

geboren op 27 oktober 1973
te Waddinxveen

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Voor Anna

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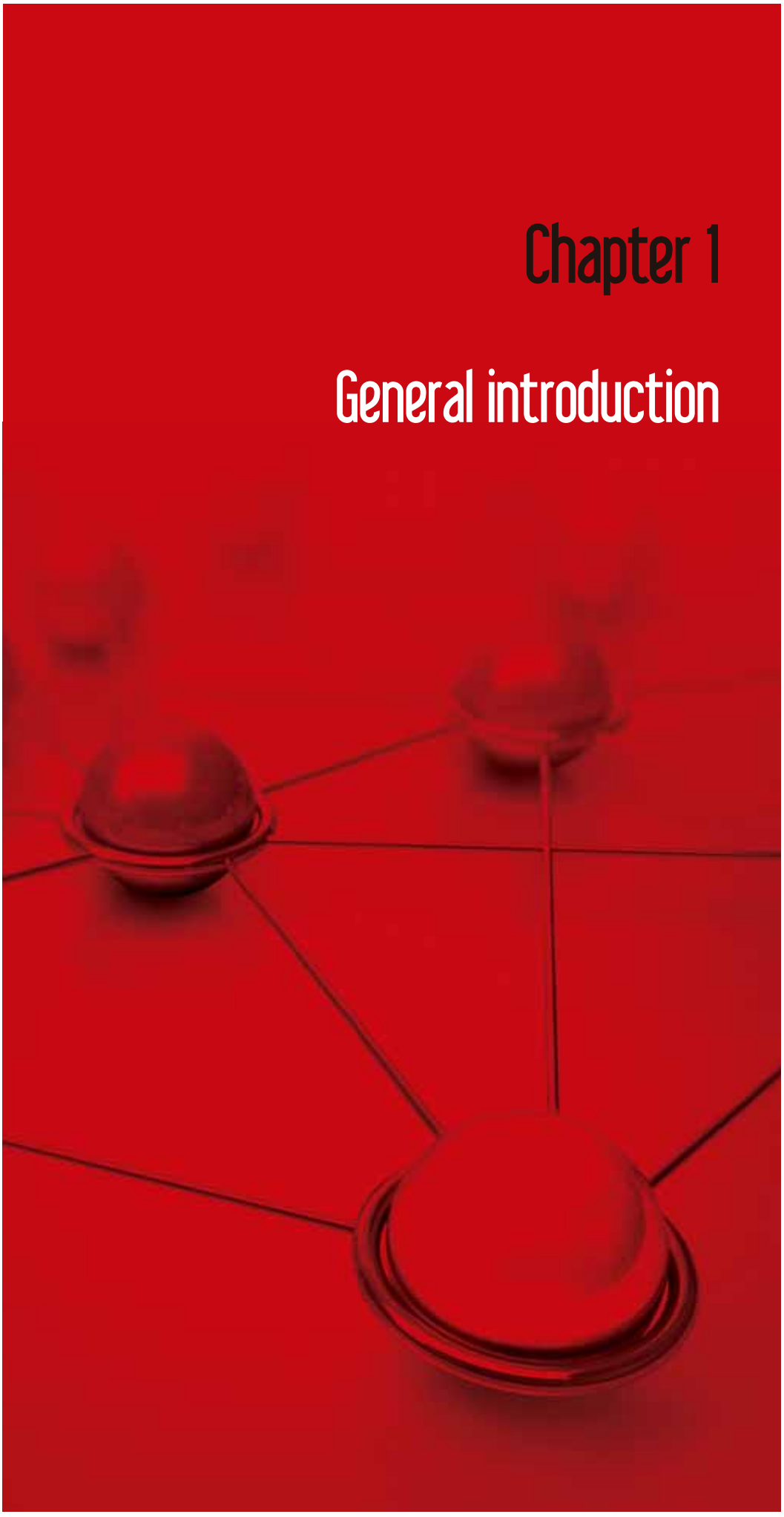
Chapter 1

General introduction



Background

Each time a healthcare professional prescribes or dispenses a drug, he or she needs to assess the benefits and risks for the individual patient. This process of decision-making, described as rational prescribing[1], is usually taken in relative uncertainty of the individual patient's benefit/risk balance. Rational prescribing to older patients is especially challenging, because their characteristics differ from those of younger adults, and available drug information to support rational prescribing is based on data of younger individuals.[2-7] Therefore, the evidence base for older people is relatively weak.

Characteristics of the older patient

Older people are more likely than younger adults to have risk factors that increase the likelihood that medications have a negative benefit/risk balance. A pivotal risk factor is the prevalence of multiple chronic conditions, such as hypertension, diabetes mellitus, and heart failure. These chronic diseases often need to be treated with medicines.[8] In the Netherlands in 2012, the number of prescriptions dispensed by community pharmacies was more than three times higher among people aged 65 years or older than that of the average inhabitant. In people aged ≥75 years it was almost five times higher.[9] Similar data have been reported in other European countries and in the USA.[10-12] The use of multiple medicines increases the risk of adverse drug reactions, because of a higher chance of drug–drug interactions or a negative impact on coexisting morbidities.[13] It has been shown that medication-related hospital admissions are more common among older individuals.[14-16]

The risk that a medicine has a negative benefit/risk balance is further increased by age-related alterations in pharmacokinetic and pharmacodynamic characteristics, such as a decline in renal function or an altered tissue distribution of drugs.[17] Drug dosages may be inadequate because of these changes, leading to a decreased effectiveness, adverse drug reactions, intoxications, or functional decline. In addition, the ageing body is less able to maintain homeostasis. This means that the chance of clinical deterioration will be greater and the decline will be more severe in older adults than in younger adults if adverse drug reactions occur.

Another risk factor concerns the practical problems older people may encounter using medications. Difficulties removing medicines from packaging, subdividing tablets, reading and understanding the labelling or patient information leaflet, and problems with the identification of medicines have been reported.[18-26] Practical problems with medication use may lead to poor medication adherence, which can also be negatively influenced by age-related cognitive decline.[20, 27] In turn, suboptimal adherence may decrease the effectiveness of a medicine or increase its risks.

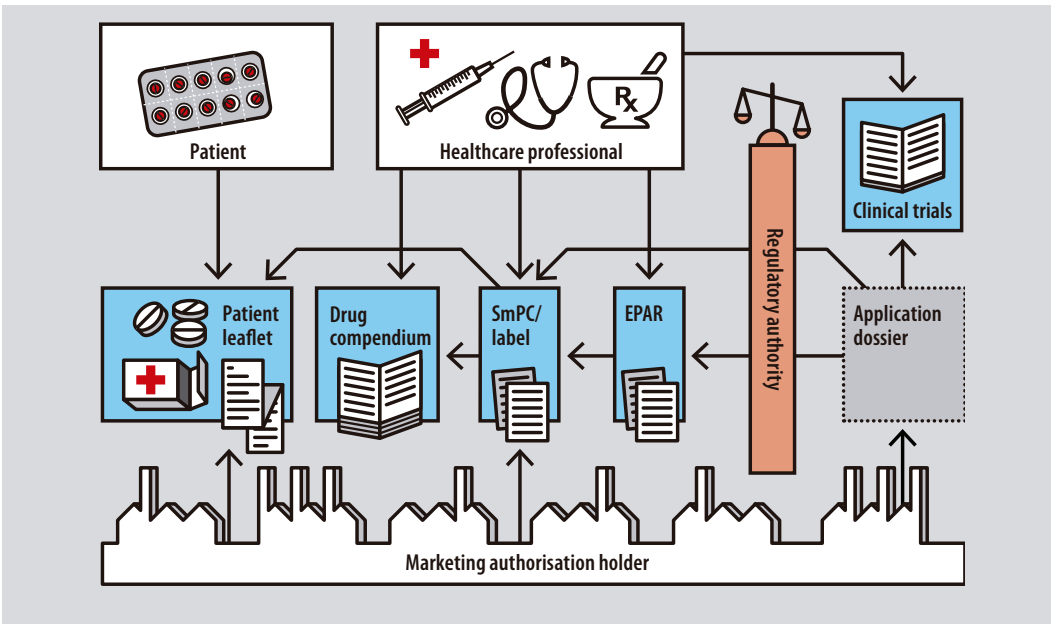
Because older people have several chronic conditions for which they use multiple medicines, they are more likely to be treated by different healthcare professionals. Risk factors associated with the healthcare system that have been identified as negatively affecting the benefit/risk balance are errors in prescribing and dispensing medication, and inadequate communication between healthcare professionals.[28-31]

The above-mentioned patient-related and healthcare system-related factors negatively influence the benefit/risk balance of medication use in older, often frail patients.[28] Therefore, it is essential for healthcare professionals to have access to evidence-based information about the benefits and risks of drugs in the older population.

Evidence base in older people

Patient-related and treatment-related risk factors, in combination with the relative lack of available information about the older population, increase uncertainty about the outcome of treatment in individual patients. Healthcare professionals need information about the benefits and risks of medication that is evidence-based and applicable to their patients. The availability of information in drug compendia, such as the Physician's Desk Reference, the British National Formulary and the Dutch *Farmacotherapeutisch Kompas*, is essential, because healthcare professionals often refer to compendia for information to support rational prescribing to older patients. This information comes from the official product information, the European summary of product characteristics (SmPC) and the US product label (PL), supplemented with information from other sources (figure 1).[32-36]

FIGURE 1 Sources of drug information



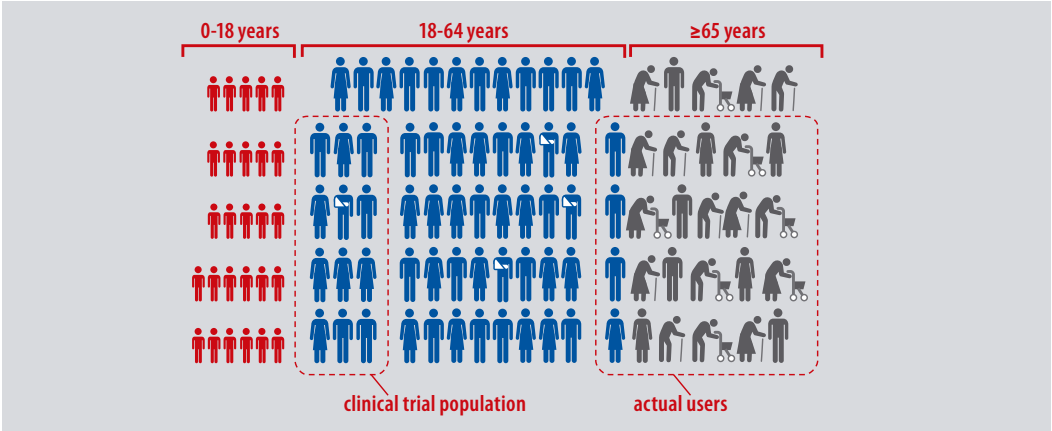
EPAR European public assessment report, SmPC summary of product characteristics

In turn, the SmPC and the PL are based on the application dossier. This dossier includes the chemical, pharmacological, and toxicity characteristics of the medicine, and reports of the animal and human studies performed, such as clinical trials investigating the efficacy and safety of the medicine.[37]

Since the application dossier is not publicly available, it is important that its contents are adequately reflected in the SmPCs, PLs, and drug compendia. It is also important that the information gathered in clinical trial populations is applicable to patients in daily practice.

Since the 1980s, the limited inclusion of older people in clinical trials of medicines intended for use in older patients, such as medication for cancer[38-41], cardiovascular disease[4, 42-45], and Parkinson's disease[46, 47], has been much discussed. In addition, the older participants that are included in trials are often not representative of the target population, because exclusion criteria are formulated to create a homogeneous trial population (figure 2).[48-53]

FIGURE 2 **Actual users compared with the clinical trial population**



A medicine is investigated in a clinical trial population that is, on average, younger and healthier than the target population that will use the medicine in daily practice.

As a result, age-related variations in disease frequency, the use of concomitant medication, and differences in pharmacokinetic and pharmacodynamic parameters are not adequately reflected in the trial population. The consequence is that the external validity of trial findings is limited with respect to the benefits and risks of a given medication in older patients.[54-56]

The limited inclusion of older people in clinical trials and the lack of representativeness of the study population are acknowledged to be a problem by the regulatory authorities and pharmaceutical industry. Since 1990, regulators and drug developers in Europe, Japan, and the USA are represented in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The aim of the

ICH is to achieve international harmonisation for the development and approval of safe, effective, and high-quality medicines in the most resource-efficient manner.[57] In order to improve the participation of older people in clinical trials, the ICH guideline on geriatrics (E7) was adopted in 1994.[58] This guideline focuses on what investigations should be carried out in older people during the pre-authorisation phase, and what information should be described in the application dossier of a new medicinal product in order to achieve market approval. The key issue is the inclusion of older people with concomitant illnesses or comedication in phase II and III trials unless there is reason to believe that inclusion may endanger the patient or lead to difficulties in interpreting the study results. In addition, the trial population should be representative of the population that will use the medicine, and trials should include a minimum number of older participants. Although it is a guideline, regulatory authorities are committed to implement the recommendations, and pharmaceutical companies have to provide convincing reasons if they do not adhere to the guideline.[57]

The information gathered in the pre-authorisation phase constitutes the basis for the assessment of the benefits and risks of a given medication for the entire population that is going to use the medicine. In this assessment, it is foreseen that certain adverse drug reactions may not be observed in the pre-authorisation phase, but can be anticipated on the basis of the drug's mechanism of action.[59] The regulatory authorities consider medicines to be suitable for the market if the benefit/risk balance is positive in the intended user population. The benefit/risk balance is periodically reassessed, since unexpected or underestimated risks may appear after marketing approval. In the post-marketing phase, evidence about the benefits and risks of medicines comes from randomised clinical trials, observational studies, and spontaneous reporting of single cases or case series.[59]

As mentioned before, application dossiers are not available to the public. However, the scientific approval process is made public in the European public assessment report (EPAR), which reflects parts of the application dossier.[60] The periodical reassessment is reflected in the periodic safety update report, composed by the pharmaceutical industry. If necessary, the SmPC and PL are updated based on information provided by the reassessment. After that, the drug compendia are updated.

Conclusion

In conclusion, it is known that older people are at greater risk of experiencing negative effects of medication as a result of patient-related and treatment-related factors. There is relatively little information available about the effectiveness and safety of drugs in older people because of the limited inclusion of this population in clinical trials. As a result, the information in the SmPCs, PLs, and drug compendia is not applicable to the older patient seen in daily practice, who often has multiple comorbidities. The adoption of the ICH E7 guideline in 1994 was intended to improve this situation.

Objectives of this thesis

The principal objective of this thesis is to investigate the current status of information for healthcare professionals to help them prescribe rationally to older people. Therefore, the first aim is to investigate the availability and clinical applicability of information for healthcare professionals. The second aim is to analyse the evidence base of information originating from clinical practice.

Outline of this thesis

In the studies reported in **Chapter 2**, the availability and clinical applicability of information are investigated. We investigate the extent to which older people are included in clinical trials (Chapter 2.1). In addition, we review the availability of information provided by such trials that can be used to support prescribing for older patients in the SmPCs (Chapter 2.2) and in national European and US drug compendia (Chapter 2.3). We also investigate what information healthcare professionals, drug developers, and regulators consider necessary to enable clinicians to prescribe rationally to older patients (Chapter 2.4).

The studies presented in **Chapter 3** describe evidence from daily practice. First, we investigate the representativeness of the clinical trial population compared with the target population in daily practice (Chapter 3.1). We then analyse adverse drug reactions that were reported after market approval (Chapter 3.2) and investigate the practical problems older people encounter in the daily use of their medication (Chapter 3.3).

In the general discussion in **Chapter 4**, we place the results of the different studies in broader perspective in relation to information about rational prescribing of medicines to older people. In addition, we give suggestions for clinical practice and future research.

References

1. Aronson JK. Rational prescribing, appropriate prescribing. *Br J Clin Pharmacol* 2004; 57(3):229-30.
2. Bartlett C, Davey P, Dieppe P, Doyal L, Ebrahim S, Egger M. Women, older persons, and ethnic minorities: factors associated with their inclusion in randomised trials of statins 1990 to 2001. *Heart* 2003; 89(3):327-8.
3. Cherubini A, Del Signore S, Ouslander J, Semla T, Michel JP. Fighting against age discrimination in clinical trials. *J Am Geriatr Soc* 2010; 58(9):1791-6.
4. Dodd KS, Saczynski JS, Zhao Y, Goldberg RJ, Gurwitz JH. Exclusion of older adults and women from recent trials of acute coronary syndromes. *J Am Geriatr Soc* 2011; 59(3):506-11.
5. McMurdo ME, Witham MD, Gillespie ND. Including older people in clinical research. *BMJ* 2005; 331(7524):1036-7.
6. McMurdo ME, Roberts H, Parker S, Wyatt N, May H, Goodman C, et al. Improving recruitment of older people to research through good practice. *Age Ageing* 2011; 40(6):659-65.
7. Witham MD, McMurdo ME. How to get older people included in clinical studies. *Drugs Aging* 2007; 24(3):187-96.
8. Antonov K, Brahm A, Carlsten A, de Joncheere K, Folino-Gallo P, Larsen L, et al. EUROMEDSTAT. The library of European Union pharmaceutical indicators: Expenditure and utilisation indicators.
9. Griens AMGF, Janssen JM, Kroon JDL, Lukaart JS, Van der Vaart RJ. Facts and figures 2013 - the year 2012 in figures. The Hague: Foundation for Pharmaceutical Statistics.
10. The Norwegian Prescription Database. (Accessed December 9, 2013, at http://www.norpd.no/).
11. Schwabe U, Paffrath D. [Prescription drugs report 2011 - Current data, costs, trends and comments]. 2011.
12. National Center for Health Statistics. Health, United States, 2012: With Special Feature on Emergency Care. Hyattsville, MD.
13. Shah BM, Hajjar ER. Polypharmacy, adverse drug reactions, and geriatric syndromes. *Clin Geriatr Med* 2012; 28(2):173-86.
14. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med* 2008; 168(17):1890-6.
15. Carrasco-Garrido P, de Andres LA, Barrera VH, de Miguel GA, Jimenez-Garcia R. Trends of adverse drug reactions related-hospitalizations in Spain (2001-2006). *BMC Health Serv Res* 2010; 10:287.
16. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; 329(7456):15-9.
17. Jansen PA, Brouwers JR. Clinical Pharmacology in Old Persons. *Scientifica (Cairo)* 2012:723678.
18. Isaac LM, Tamblyn RM. Compliance and cognitive function: a methodological approach to measuring unintentional errors in medication compliance in the elderly. McGill-Calgary Drug Research Team. *Gerontologist* 1993; 33(6):772-81.
19. Atkin PA, Finnegan TP, Ogle SJ, Shenfield GM. Functional ability of patients to manage medication packaging: a survey of geriatric inpatients. *Age Ageing* 1994; 23(2):113-6.
20. Kairuz T, Bye L, Birdsall R, Deng T, Man L, Ross A, et al. Identifying compliance issues with prescription medicines among older people: a pilot study. *Drugs Aging* 2008; 25(2):153-62.
21. Kelly J, D'Cruz G, Wright D. Patients with dysphagia: experiences of taking medication. *J Adv Nurs* 2010; 66(1):82-91.

22. Nikolaus T, Kruse W, Bach M, Specht-Leible N, Oster P, Schlierf G. Elderly patients' problems with medication. An in-hospital and follow-up study. *Eur J Clin Pharmacol* 1996; 49(4):255-9.
23. Ostrom JR, Hammarlund ER, Christensen DB, Plein JB, Kethley AJ. Medication usage in an elderly population. *Med Care* 1985; 23(2):157-64.
24. Overgaard AB, Hojsted J, Hansen R, Moller-Sonnergaard J, Christrup LL. Patients' evaluation of shape, size and colour of solid dosage forms. *Pharm World Sci* 2001; 23(5):185-8.
25. Ruscin JM, Semla TP. Assessment of medication management skills in older outpatients. *Ann Pharmacother* 1996; 30(10):1083-8.
26. Tordoff J, Simonsen K, Thomson WM, Norris PT. "It's just routine." A qualitative study of medicine-taking amongst older people in New Zealand. *Pharm World Sci* 2010; 32(2):154-61.
27. Thwaites JH. Practical aspects of drug treatment in elderly patients with mobility problems. *Drugs Aging* 1999; 14(2):105-14.
28. Drenth-van Maanen AC. General introduction. Appropriate prescribing for older people. Enschede; 2013. p. 9-16.
29. Vingerhoets RW, Wieringa MH, Egberts TCG, Jansen MMPM, Jansen PAF. Multiple physicians are not independently associated with inappropriate prescribing: a cross-sectional study of geriatric patients. *Br J Clin Pharmacol* 2014;77(1):213-5.
30. Van der Linden CM, Jansen PA, van Marum RJ, Grouls RJ, Korsten EH, Egberts AC. Recurrence of adverse drug reactions following inappropriate re-prescription: better documentation, availability of information and monitoring are needed. *Drug Saf* 2010; 33(7):535-8.
31. Van der Linden CM, Kerskes MC, Bijl AM, Maas HA, Egberts AC, Jansen PA. Represcription after adverse drug reaction in the elderly: a descriptive study. *Arch Intern Med* 2006; 166(15):1666-7.
32. Health Care Insurance Board. Pharmacotherapeutic Compass. (Accessed December 9, 2013, at http://www.fk.cvz.nl/).
33. British National Formulary. London: Joint Formulary Committee. (Accessed January, 2013, at http://www.medicinescomplete.com).
34. PDR Network. Physicians' Desk Reference. (Accessed December 9, 2013, at http://www.pdr.net/).
35. European Commission. A guideline on summary of product characteristics. (Accessed December 9, 2013, at http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf).
36. Food and Drug Administration (FDA). Labeling for human prescription drug and biological products - Implementing the new content and format requirements – Draft guidance. (Accessed December 9, 2013, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf).
37. Dutch Medicines Evaluation Board. What does a marketing authorisation dossier contain? (Accessed December 9, 2013, at http://www.cbg-meb.nl/CBG/en/human-medicines/consumers/organisation-around-medicines/What-does-a-marketing-authorisation-dossier-contain/default.htm).
38. Yonemori K, Hirakawa A, Komiyama N, Kouno T, Ando M, Fujiwara Y, et al. Participation of elderly patients in registration trials for oncology drug applications in Japan. *Ann Oncol* 2010; 21(10):2112-8.
39. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004; 22(22):4626-31.
40. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: known problem, little progress. *J Clin Oncol* 2012; 30(17):2036-8.
41. Hutchins LF, Unger JM, Crowley JJ, Coltman Jr. CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999; 341(27):2061-7.

42. Foerch C, Czapowski D, Misselwitz B, Steinmetz H, Neumann-Haefelin T, Arbeitsgruppe Schlaganfall Hessen (ASH). Gender imbalances induced by age limits in stroke trials. *Neuroepidemiology* 2010; 35(3):226-30.

43. Green P, Maurer MS, Foody JM, Forman DE, Wenger NK. Representation of older adults in the late-breaking clinical trials American Heart Association 2011 Scientific Sessions. *J Am Coll Cardiol* 2012; 60(9):869-71.

44. Kitzman DW, Rich MW. Age disparities in heart failure research. *JAMA* 2010; 304(17):1950-1.

45. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011; 171(6):550-6.

46. Fitzsimmons PR, Blayney S, Mina-Corkill S, Scott GO. Older participants are frequently excluded from Parkinson's disease research. *Parkinsonism Relat Disord* 2012;18(5):585-9.

47. Mitchell SL, Sullivan EA, Lipsitz LA. Exclusion of elderly subjects from clinical trials for Parkinson disease. *Arch Neurol* 1997; 54(11):1393-8.

48. Al-Refaie WB, Vickers SM, Zhong W, Parsons H, Rothenberger D, Habermann EB. Cancer trials versus the real world in the United States. *Ann Surg* 2011; 254(3):438-42.

49. Dowd R, Recker RR, Heaney RP. Study subjects and ordinary patients. *Osteoporos Int* 2000; 11(6):533-6.

50. Hori A, Shibata T, Kami M, Kusumi E, Narimatsu H, Kishi Y, et al. Age disparity between a cancer population and participants in clinical trials submitted as a new drug application of anticancer drugs in Japan. *Cancer* 2007; 109(12):2541-6.

51. Sharpe N. Clinical trials and the real world: selection bias and generalisability of trial results. *Cardiovasc Drugs Ther* 2002; 16(1):75-7.

52. Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry* 2002; 159(3):469-73.

53. Uijen AA, Bakx JC, Mokkink HG, van Weel C. Hypertension patients participating in trials differ in many aspects from patients treated in general practices. *J Clin Epidemiol* 2007; 60(4):330-5.

54. Saunders C, Byrne CD, Guthrie B, Lindsay RS, McKnight JA, Philip S, et al. External validity of randomised controlled trials of glycaemic control and vascular disease: how representative are participants? *Diabet Med* 2013; 30(3):300-8.

55. Steg PG, Lopez-Sendon J, Lopez de Sa E, Goodman SG, Gore JM, Anderson FA Jr, et al. External validity of clinical trials in acute myocardial infarction. *Arch Intern Med* 2007; 167(1):68-73.

56. Travers J, Marsh S, Caldwell B, Williams M, Aldington S, Weatherall M, et al. External validity of randomised controlled trials in COPD. *Respir Med* 2007; 101(6):1313-20.

57. ICH official website. (Accessed December 9, 2013, at http://www.ich.org/).

58. European Medicines Agency. Studies in support of special populations: geriatrics ICH E7 (CPMP/ICH/379/95). (Accessed December 9, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002875.pdf).

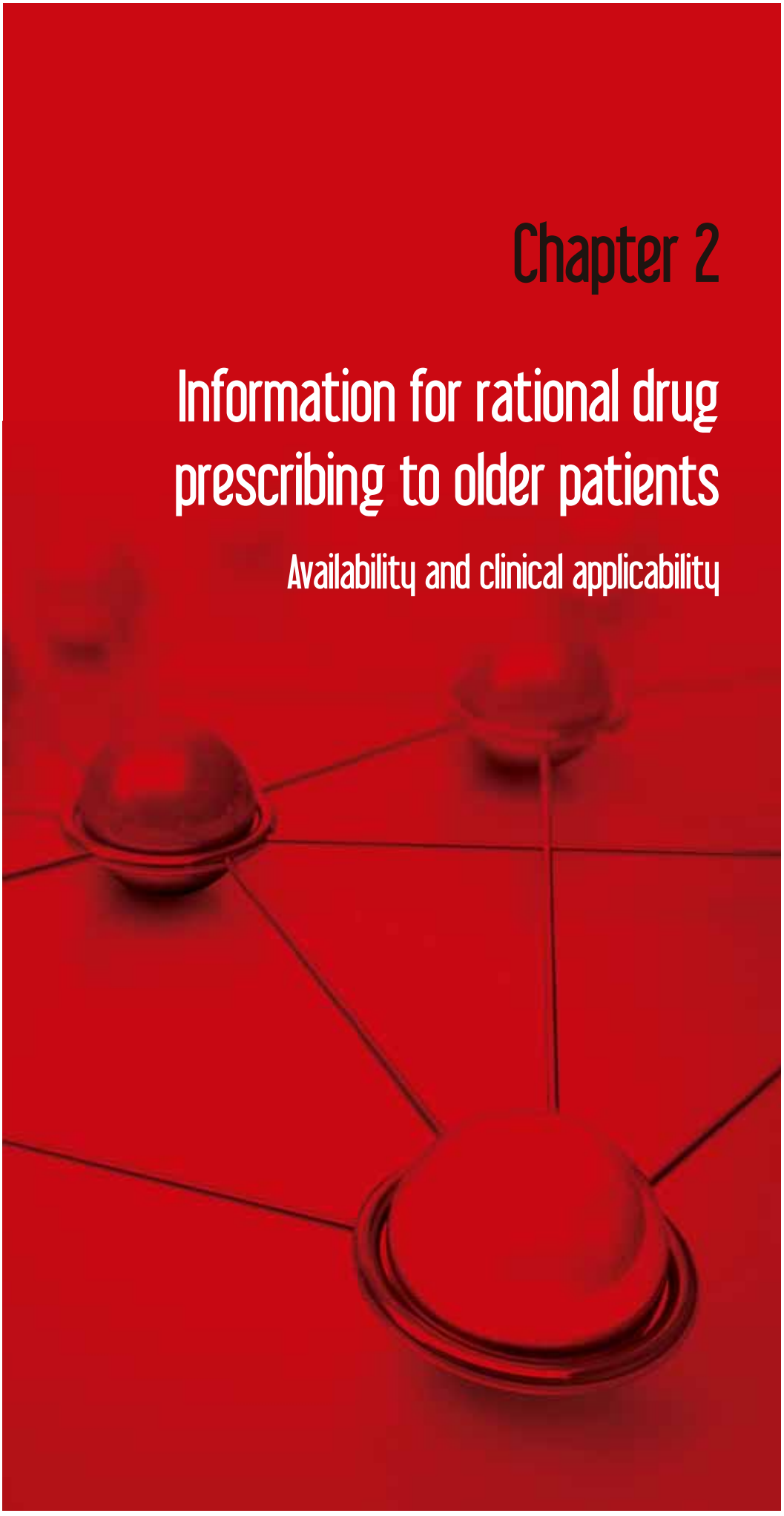
59. Curtin F, Schulz P. Assessing the benefit: risk ratio of a drug - randomised and naturalistic evidence. *Dialogues Clin Neurosci* 2011; 13(2):183-90.

60. Website European Medicines Agency. European public assessment reports. (Accessed December 9, 2013, at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124).

Chapter 2

Information for rational drug prescribing to older patients

Availability and clinical applicability

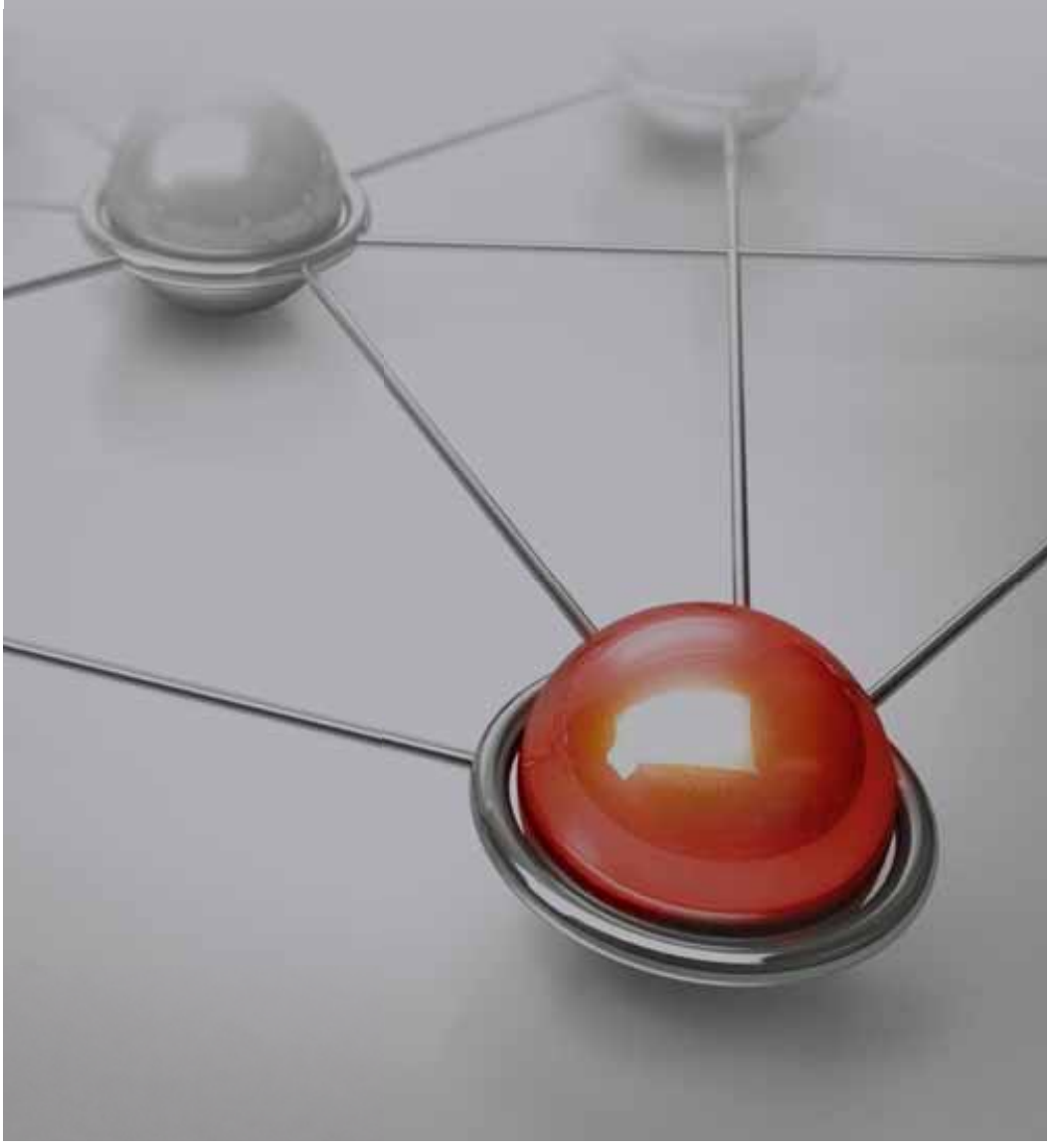


2.1

Participation of older people in pre-authorisation trials of recently approved medicines

Erna Beers, Dineke C. Moerkerken, Hubert G.M. Leufkens, Toine C.G. Egberts, Paul A.F. Jansen

Submitted



Abstract

Introduction To improve the inclusion of older people in clinical trials, regulators and drug developers have created the ICH E7 guideline. It states that at least 50% of participants should be aged ≥65 years for medicines specifically indicated for older people and >100 subjects should be aged ≥65 years for medicines intended for younger as well as older people. The objective was to investigate the inclusion of older people in clinical trials of recently authorised medicines, evaluating the adherence to the ICH E7 guideline.

Methods European public assessment reports, published clinical trials, and the WHO International Clinical Trials Registry Platform. Main outcome measures were the number and proportion of randomised participants aged ≥65 and ≥75 years and all inclusion and exclusion criteria of studies of drugs for diseases characteristically associated with aging (venous thromboembolism after replacement arthroplasty, osteoporosis, atrial fibrillation) and diseases that are common in, but not unique, to older patients (type 2 diabetes mellitus, depression, bipolar disorder, epilepsy).

Results In 114 phase II and III trials of 12 medicines, 43% of participants were aged ≥65 years; 16% were ≥75 years. In trials involving diseases characteristically associated with aging, 57% of subjects were aged ≥65; 22% were ≥75 years. In trials involving diseases not unique to old age, 9% of subjects were aged ≥65; 1% were ≥75 years. 31% of the trials applied upper age limits. The frequency of exclusion based on upper age limit was significantly lower in trials involving diseases characteristically associated with aging compared with trials of diseases not unique to old age (18% vs. 45%; p=.002). Exclusion criteria were based on comorbidity (75%), concomitant medication (72%), and other criteria correlated with advancing age (61%). These criteria were applied more frequently in larger trials (>500 participants; p<.02).

Conclusions Studies of diseases not uniquely associated with old age included an unacceptably low proportion of older people, contrary to the recommendations of the ICH E7 guideline. Although the proportion of older participants in trials of diseases characteristically associated with aging was appropriate for certain medicines, the use of age-sensitive exclusion criteria limited the representativeness of the trial population.

Introduction

The limited inclusion of older people in clinical trials of medicines intended for use in older patients, such as drugs for cancer, cardiovascular disease, and Parkinson's disease, has been much discussed.[1-18] This limited inclusion affects the generalizability of the efficacy and safety findings, especially as most older patients have multiple comorbid conditions for which they use several drugs, and have pharmacokinetic and pharmacodynamic characteristics different from those of younger individuals.[19]

To improve the representation of older people in clinical trials, the International Conference on Harmonization (ICH) guideline on geriatrics (E7) was adopted in 1994 by the regulatory bodies of the European Union, Japan and the USA.[20] The guideline states that advanced age or the presence of concomitant illnesses or comedication is no longer a justifiable basis for excluding patients from phase II and III trials unless there is reason to believe that inclusion may endanger the patient or lead to difficulties in interpreting the study results. In addition, the trial population should be representative of the population that will use the drug, and trials should include a minimum number of older participants. For medicines intended for diseases characteristically associated with old age, ≥50% of the participants should be ≥65 years. For medicines intended to treat diseases present in, but not unique to, older people, >100 participants aged ≥65 years should be included.

In 2006, the European Medicines Agency (EMA) evaluated ten registration dossiers of medicines for diseases common in older individuals that had been recently marketed in Europe. Most dossiers were moderately compliant with the ICH E7 recommendations, even when the medicines concerned would be used to treat diseases specifically associated with aging.[21] Other studies revealed that upper age limits were being applied in approximately a quarter of the trials of the treatment of acute coronary syndrome and heart failure, and in as many as half of the trials investigating the treatment of Parkinson's disease.[1,3,7,22] In addition, at least one poorly justified exclusion criterion was present in 84% of clinical trials published in high impact journals, regardless of the condition or disease being investigated, in 80% of type 2 diabetes trials and in 43% of heart failure trials registered with the WHO International Clinical Trials Registry Platform (WHO-ICTRP).[7,23,24] Since heart failure is a condition characteristically associated with aging, whereas type 2 diabetes mellitus is also present in younger people, it would appear that different exclusion criteria, in number and content, are used for therapeutic indications that are characteristically associated with aging and for indications not unique to old age.

Therefore, this study investigates the extent to which older people are included in clinical trials of recently authorised medicines for diseases characteristically associated with older age or for diseases that are common in, but not unique to, old age, thereby evaluating adherence to the ICH E7 guideline.

Methods

Selection of medicines and trials

The medicines included were granted marketing authorisation by the EMA between 1 January 2008 and 1 January 2011 and were indicated for diseases characteristically associated with aging (venous thromboembolism after replacement arthroplasty, osteoporosis, atrial fibrillation) and diseases common in, but not unique to, older patients (type 2 diabetes mellitus, depression, bipolar disorder, epilepsy). The first four indications were selected because older individuals are typically affected by these conditions; type 2 diabetes mellitus was selected because the majority of the patient population is older than 65 years,[25] and the latter three indications because older people are susceptible to adverse effects related to centrally acting medicines.

Because the ICH E7 guideline states that older people need to be adequately represented in phase II and phase III trials, all primary, i.e. not extension, phase II and phase III trials were identified in the European public assessment reports (EPARs) for the approved medicines. The EPAR is publicly available on the EMA website once a drug is authorised and reflects the scientific conclusion of the European Commission.[26] It contains parts of the pre-authorisation dossier. As the latter is not publicly available, the EPAR is the closest publicly available source to this dossier.

Data source and data extraction

Three data sources were used in order to retrieve as much relevant data on the performed trials as possible: the EPAR, the WHO-ICTRP[27] and Pubmed. WHO-ICTRP collects data from national and regional registers of clinical studies, including the US National Institute of Health Clinical Trials Registry.[28] The study protocol and, if available, the results of the study were extracted from the trial registry and were examined to verify data and obtain additional data. PubMed was also used to verify data and obtain additional data.

The following variables were retrieved in July 2012: trial phase (II and/or III), trial start date, number of participating centres and countries, the total number of randomised participants, the number of randomised participants aged ≥65 years and ≥75 years, and all inclusion and exclusion criteria. If the number of randomised patients was not available, the number of the safety population or the number from other defined populations was extracted. Exclusion criteria were defined as criteria limiting the participation of individuals, whereas inclusion criteria were those determining the recruitment of patients with the condition of interest. For example, the following inclusion criteria were given for a trial of osteoporosis treatment: "Postmenopausal women up to 80 years of age were eligible if they had a bone mineral density T score of −1.8 to −4.0 at the lumbar spine or −1.8 to −3.5 at either the femoral neck or total hip. An upper limit of −1.8 was selected to include subjects with both osteopenia and osteoporosis."[29] According to Van Spall *et al.*[24] postmenopausal status was considered an exclusion criterion as premenopausal women affected by osteoporosis will receive the same treatment as those with postmenopausal osteoporosis. For the same reason, the age cut-off was considered an exclusion criterion for older patients.

If the three sources gave different numbers of participants as being randomised, the data from the published trials were considered most accurate, followed by the data from the WHO-ICTRP and the EPARs, respectively.

Data analysis

Descriptive data are presented as means or medians, where appropriate, for continuous variables and as number and frequencies for categorical variables. For univariate analyses, the Mann-Whitney U test was used for continuous data (age limits), since age was not normally distributed, as analysed with Kolmogorov-Smirnov and Shapiro-Wilk tests. The Pearson Chi-square test or Fisher's exact test was used for categorical variables in case of small numbers (expected values <5). All statistical tests were 2-tailed. Factors were considered statistically significant at $p < .05$. Data were analysed using statistical software (SPSS, version 20; SPSS Inc., Chicago, Illinois).

Results

Twelve medicines were included: dabigatran and rivaroxaban for the prevention of venous thromboembolism after replacement arthroplasty; lasofoxifene, bazedoxifene, and denosumab for osteoporosis; dronedarone and vernakalant for atrial fibrillation; liraglutide and saxagliptin for type II diabetes mellitus; agomelatine for depression; asenapine for bipolar disorder; and eslicarbazepine for epilepsy. In the pre-authorisation phase, 114 trials were performed: 45 phase II and 69 phase III trials. Most trials were initiated between 2003 and 2005 (n=40; 35.1%) (table 1). Overall, 88,261 participants were randomised, with a median number of 423 per trial (range 19–8556) (table 2).

All trials were mentioned in the EPARs, but information about exclusion criteria was missing in all phase II trials and in 33 (47.8%) of the phase III trials. Twenty-five (55.5%) phase II trials were published, and 23 (51.1%) were registered in the WHO-ICTRP; 50 (72.5%) of phase III trials were published and 55 (79.7%) were registered in the WHO-ICTRP. All three sources provided information about 28 (62.2%) phase II trials and 58 (84.1%) phase III trials.

Number of older subjects

Fifty-three (46.5%) trials provided information about the number or proportion of randomised participants aged ≥65 years, and 58 (50.9%) provided information about the number and proportion of participants aged ≥75 years (table 2). Overall, 19,677 (43.1%) participants were aged ≥65 years, and 8,021 (16.1%) were aged ≥75 years (figure 1). The majority were involved in trials of diseases characteristically associated with aging (n=18,483). The largest population of older participants was found in the trials of dabigatran and rivaroxaban. The osteoporosis trials either did not provide information about the number or proportion of older subjects (lasofoxifene), excluded subjects aged ≥65 years in the sole trial that provided such information (bazedoxifene), or had a focus on older people (denosumab). In the trials of treatments for diseases not unique to, but present in, old age, 9% of the trial population

TABLE 1 Trial characteristics

Characteristic	Overall (n=114)	Phase II (n=45)	Phase III* (n=69)
Design and setting			
Single centre, % (n)	2.6 (3)	6.7 (3)	-
Multicentre, % (n)	77.2 (88)	60.0 (27)	88.4 (61)
Unknown, % (n)	20.2 (23)	33.3 (15)	11.6 (8)
Single country, % (n)	9.6 (11)	20.0 (9)	2.9 (2)
More than one country, % (n)	64.9 (74)	44.4 (20)	78.3 (54)
Unknown, % (n)	25.5 (29)	35.6 (16)	18.8 (13)
Median number of countries, range	6 (1–37)	3 (1–19)	8.5 (1–37)
Trial location, % (n)			
European Union[a]	25.5 (29)	28.9 (13)	23.2 (16)
European Union and North America[b]	26.3 (30)	11.1 (5)	36.2 (25)
North America[c]	17.5 (20)	17.8 (8)	17.4 (12)
Other countries[d]	1.8 (2)	4.4 (2)	-
Unknown	28.9 (33)	37.8 (17)	23.2 (16)
Start date trial, % (n)			
2000–2002	14.0 (16)	15.6 (7)	13.0 (9)
2003–2005	35.1 (40)	28.9 (13)	39.1 (27)
2006–2008	17.6 (20)	2.2 (1)	27.6 (19)
Unknown	33.3 (38)	53.3 (24)	20.3 (14)

* One phase II/III trial was analysed as a phase III trial; [a] Clinical trials conducted in the European Union or in the European Union and other countries but not North America; [b] Clinical trials conducted in the European Union and North America or in the European Union, North America and other countries; [c] Clinical trials conducted in North America or in North America and other countries but not the European Union; [d] Clinical trials conducted neither in European Union nor in North America.

consisted of subjects aged ≥65 years and 1% of subjects aged ≥75 years. The trials of drugs for type 2 diabetes included >100 older participants; these accounted for less than 20% of the overall trial population. The asenapine (bipolar disorder) and eslicarbazepine (epilepsy) trials randomised 49 and 14 subjects aged ≥65 years; they did not include subjects ≥75 years.

Exclusion criteria

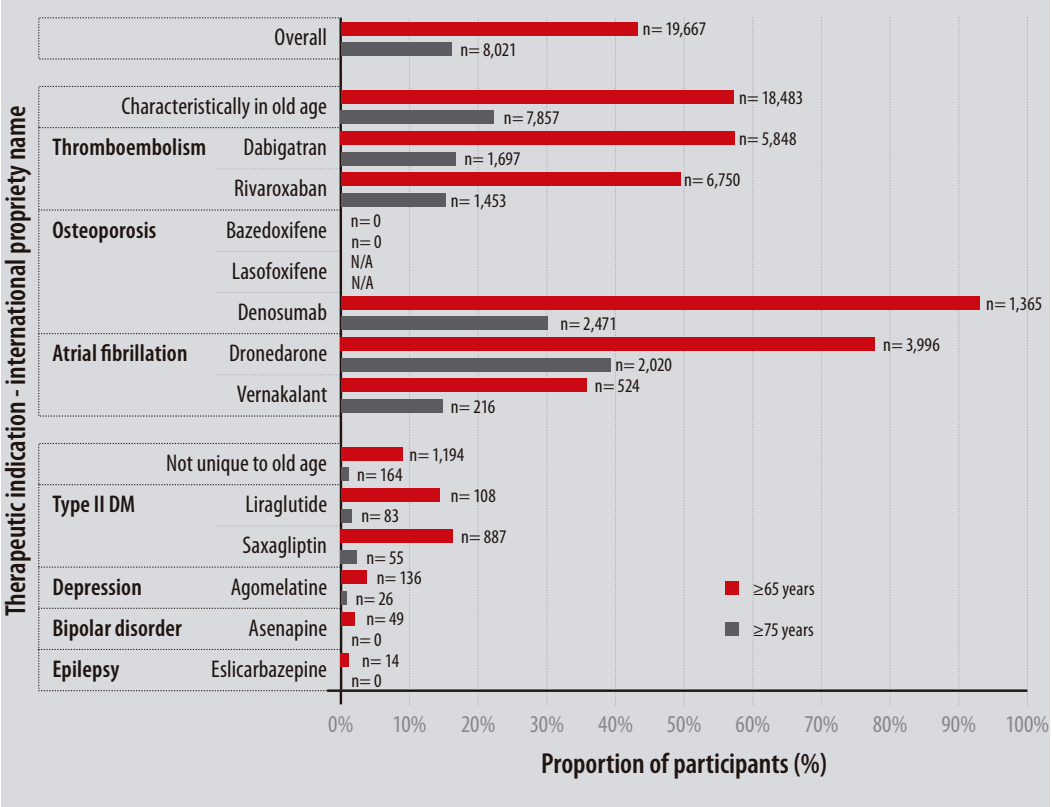
Upper age limits were applied in 35 (30.7%) trials (table 3), with a median upper age limit of 77 years (range 65–90). Comorbidities were reason for exclusion in 75.4% (n=86) of the trials, with unspecified medical conditions, such as "not healthy" or "a severe unstable disease", being mentioned in 64 (56.1%) trials. Medication-related exclusion criteria, such as the use of concomitant medication, or past history of specified adverse events were mentioned in 82 (71.9%) trials. Other exclusion criteria that could adversely affect the inclusion of older people were the inability to give informed consent in 30 trials (26.3%), cognitive impairment in 4 trials (3.5%), decreased life expectancy in 3 trials (2.6%), and communication or language barriers in 4 trials (3.5%). A statement about the assent of the eligible subject in combina-

TABLE 2 Trials and randomised patients per medicine

Approved therapeutic indication / international propriety name	Number of trials – overall	Number of randomised participants – overall	Number of trials providing information about participants aged 65+	Overall number of randomised patients in these trials	Number of trials providing information about participants aged 75+	Overall number of randomised patients in these trials
Overall, n (%)	114	88,261	53 (46.5)	45,697 (51.8)	58 (50.9)	49,890 (56.5)
Median number per trial, range		423 (19–8,556)				
Therapeutic indications characteristically associated with aging						
Prevention venous thromboembolism	**13**	**23,777**	**13**	**23,777**	**7**	**19,764**
Dabigatran	4	10,183	4	10,183	4	10,183
Rivaroxaban	9	13,594	9	13,594	3	9,581
Osteoporosis	**32**	**33,109**	**2**	**1,962**	**4**	**8,660**
Bazedoxifene	5	10,660	1	494	1	494
Lasofoxifene	16*	9,644*	0	-	0	-
Denosumab	11	12,805	1	1,468	3	8,166
Atrial fibrillation	**16**	**8,958**	**10**	**6,595**	**10**	**6,595**
Dronedarone	8	7,495	2	5,132	2	5,132
Vernakalant	8	1,463	8	1,463	8	1,463
Therapeutic indications not unique to, but present in, older people						
Type 2 diabetes mellitus	**21**	**10,883**	**9**	**6,163**	**17**	**7,731**
Liraglutide	12	5,430	1	746	12	5,430
Saxagliptin	9	5,453	8	5,417	5	2,301
Depressive disorder – agomelatine	**13**	**4,614**	**10**	**3,522**	**11**	**3,889**
Bipolar disorder – asenapine maleate	**12**	**5,496**	**5**	**2,484**	**5**	**2,057**
Epilepsy – eslicarbazepine	**7**	**1,424**	**4**	**1,194**	**4**	**1,194**

* Numbers were provided in 2 out of 10 phase II trials and 2 out of 6 phase III trials.

FIGURE 1 **Overall number and proportion of older participants in the clinical trials that provided information**



The numbers and proportions are based on the trials that provided information about participants aged ≥65 and ≥75 years as shown in table 2.

N/A Not applicable; DM diabetes mellitus

tion with the assent and consent of the legal representative was not mentioned as eligibility criterion in any of the trials.

Subgroup analyses

Larger trials (>500 participants) provided information about upper age limits more often than did smaller trials (97.6% vs. 81.7%; p=.025) (table 4). The frequency of excluding older participants based on age did not differ between smaller and larger trials (35.0% vs. 34.1%; p=.363). However, exclusion based on comorbidity (95.1% vs. 76.7%; p=.013), concomitant medication (92.7% vs. 73.3%; p=.015) and other criteria strongly associated with advancing age (48.8% vs. 18.3%; p=.001) was more common in larger trials than in smaller trials. Upper age limits were significantly less common in trials of medicines for diseases characteristic of aging than in trials of medicines for diseases not unique to, but present in, old age (18.0% vs. 45.3%; p=.002), with an upper age limit of 80 years (range 65–90) for indications typically associated with aging and 76.5 years (range 65–80) for indications present in old age (p=.028).

TABLE 3 Frequency of exclusion criteria

Exclusion criterion	Overall frequency, % (n)* n=114
Information available about upper age limit	75.4 (86)
Trials that applied an upper age limit	**30.7 (35)**
Upper age limit, median (range)	77 (65–90)
65–74 years	9.6 (11)
75–84 years	16.7 (19)
≥ 85 years	4.4 (5)
Comorbidity	**75.4 (86)**
Unspecified medical condition	56.1 (64)
Renal	38.6 (44)
Hepatic	37.7 (43)
Cardiovascular	45.6 (52)
Endocrine	39.5 (45)
Malignancy	26.3 (30)
Haematological	25.4 (29)
Psychiatric	22.8 (26)
Neurologic	9.6 (11)
Pulmonary	5.3 (6)
Musculoskeletal	14.0 (16)
Other	60.5 (69)
Concomitant medication	**71.9 (82)**
Hypersensitivity to (study) medication	24.6 (28)
Other exclusion criteria strongly correlated to advancing age	**60.5 (69)**
Inability to give informed consent	26.3 (30)
Cognitive impairment	3.5 (4)
Physical disability or functional status	0 (0)
Decreased life expectancy	2.6 (3)
Communication or language barrier	3.5 (4)

* Specified if other measures were used.

TABLE 4 Frequency of exclusion criteria – subgroup analyses

Exclusion criterion	Sample size ≤ 500, % (n)* n=60	Sample size > 500, % (n)* n=41	p value	Indications characteristically associated with aging, % (n)* n=61	Indications not unique to older people, % (n)* n=53	p value
Information available about upper age limit	81.7 (49)	97.6 (40)	**.025**	73.8 (45)	86.8 (46)	.084
Exclusions based on upper age limit	35.0 (21)	34.1 (14)	.363	18.0 (11)	45.3 (24)	**.002**
Upper age limit, median (range)	75 (65–90)	80 (66–90)	.820	80 (65–90)	76.5 (65–80)	**.028**
Comorbidity	76.7 (46)	95.1 (39)	**.013**	72.1 (44)	79.2 (42)	.379
Concomitant medication	73.3 (44)	92.7 (38)	**.015**	70.5 (43)	75.5 (40)	.551
Other exclusion criteria related to age†	18.3 (11)	48.8 (20)	**.001**	31.1 (19)	24.5 (13)	.433

* Specified if other measures were used; † Inability to give informed consent, cognitive impairment, physical disability or functional status, decreased life expectancy, communication or language barrier.

Discussion

The overall findings show that the number of older subjects randomised in clinical trials corresponded fairly well with the proportion in the general population in Western Europe and the United States, namely, 43% of the subjects were aged ≥65 years, compared with 30% in the general population, and 16% of the participants were aged ≥75 years, compared with 20% in the general population.[30] These figures were positively skewed by the proportion of older people randomised to trials of medicines for diseases characteristically associated with aging, since more than 50% of the participants were aged ≥65 years and more than 20% were aged ≥75 years. The absolute number of older subjects included (almost 20,000 participants aged ≥65 years and more than 8000 subjects aged ≥75) is promising as it shows that it is possible to recruit older subjects. However, the proportion of older subjects included in trials of medicines for diseases not unique to, but present in, old age was less optimistic, with less than 10% of the randomised participants being aged ≥65 years and only 1% being ≥75 years.

The low proportion of older participants included in type 2 diabetes trials is surprising, given that most people with diabetes in developed countries are >65 years and that 15% are >80 years.[25] The failure to include participants aged ≥75 years in epilepsy trials is also striking, because a quarter of patients with epileptic seizures are ≥60 years and more than 10% are ≥70 years.[31] Although the aetiology of epileptic seizures in older patients is different from that in children, the treatment options are the same and the failure to include older participants in these trials can be considered an omission. The same is true for the osteoporosis trials, since the sole bazedoxifene trial that provided information about the number of older subjects

used an upper age limit of 65 years. This does not necessarily mean that older people have been excluded in all bazedoxifene trials - it is possible that the other four trials included older subjects, but they failed to provide relevant data. The sole denosumab trial that provided information about the number of participants aged ≥65 years was a trial specifically aimed at older subjects; the other 10 trials did not provide data on the number of older participants. The lasofoxifene trials provided very few data about the number or proportion of older subjects. The reason for this is not known, but the drug has not been marketed in Europe since its initial marketing authorisation in 2009. Consequently, the marketing authorisation is no longer valid.[32]

Upper age limits were applied in almost one-third of all trials, and more often in trials of medicines for conditions not unique to old age (45% vs. 18%). Other studies found that upper age limits were used in 25% of atrial fibrillation trials and in 49% of Parkinson trials, both diseases typically associated with aging, and in 66% of type 2 diabetes trials, a disease not unique to old age.[1,7,23]

Although the number of older participants randomised in trials of some therapeutic indications was consistent with ICH E7 recommendations, many studies used exclusion criteria that indirectly affect the inclusion of older people, such as the use of concomitant medication, comorbidities, and e.g., inability to give informed consent and communication barriers. These criteria affect the representativeness of the study population. Of the studies reviewed, 75% used comorbidity as exclusion criterion, a proportion similar to that (77–81%) reported in previous studies.[7,23,24] Other studies found a lower frequency of exclusion based on concomitant medication, but these studies investigated pharmacological and non-pharmacological trials.[7,23,24] In the latter, medication use might be considered less of a concern. The inability to give informed consent was mentioned in 26% of the included studies, compared to 11% and 86% in other studies.[24,33] Limited life expectancy was an exclusion criterion in 3% of the included studies, compared with 9–36% in other studies.[7,23,24,33] Overall, 4% of studies excluded participants because of cognitive impairment, a lower proportion than seen in type 2 diabetes trials (13%) and heart failure trials (18%).[7,23] Lastly, broad exclusion criteria, such as 'any serious medical condition', were used in 56% of the investigated trials compared with 10–54% in other studies.[7,23,24]

Certain exclusion criteria are justified, e.g., the exclusion of subjects with a bleeding risk in trials investigating anticoagulant drugs. However, several studies found at least one poorly justified exclusion criterion being used in 84% of clinical trials published between 1994 and 2006, and in 43% of ongoing atrial fibrillation trials in 2008 and in 80% of the ongoing diabetes trials in 2011, registered in the WHO-ICTRP.[7,23,24] In the current study, such an evaluation was not performed, because while individual criteria might not be justified, their combination might fully justify the exclusion of certain older individuals.

This study had a number of limitations. First, only those trials that specifically mentioned the number and proportion of older individuals were analysed on those parameters, slightly more than 50%; trials that provided a mean or median age with dispersion values were not taken into account. This choice was made on the assumption that the age distribution in

trials is not Gaussian, because of the disproportionate exclusion of older subjects. Other studies have estimated the number of older subjects, using data for the mean or median age and dispersion values, or have tried to correct for the non-Gaussian distribution by using truncated normal distributions.[21,34] Secondly, the focus was on randomised subjects, since trials usually provide information about this population; however, it is not clear how many older subjects were actually exposed to trial medication. Thirdly, as twelve medicines were included, the number of trials per therapeutic indication was limited. And lastly, since the exclusion criteria used varied greatly between trials, and some criteria were not used in all trials, it is likely that exclusion criteria were underreported. This limitation has been supposed before.[24]

A strength of the current study is that different data sources were used. The EPAR, published by the EMA, is the publically available document that is closest in content to the registration dossier, and thus has the highest likelihood of reporting pre-authorisation trials. This assumption was confirmed, since 114 trials were identified in the EPARs, compared with 88 trials in the WHO-ICTRP and Pubmed. In addition, the use of different sources of information limited the likelihood of publication bias or the use of incomplete databases, as recognised previously.[1,7,23] Second, this study evaluated the inclusion of older people in phase II trials, as required in the ICH E7 guideline[20], and compared drug trials for indications specifically and not uniquely associated with old age, neither of which has been done before.

The underrepresentation of older subjects in trials can have safety implications, since trial results obtained in a selected, relatively young and healthy population are applied to older patients in daily practice.[34,35] The key issue is to improve the inclusion of older participants representative of the target population in clinical trials, which is a task for all stakeholders, not only drug developers and regulators, but also research ethics committees, sponsors, researchers, healthcare professionals, medical journal editors, and last but not least, older people and their carers or legal representatives. Steps have been taken to improve the representativeness of older trial participants, such as the regulatory geriatric medicines strategy, the PREDICT charter and the ethical guidance for good clinical practice, as recently published by the European Forum for Good Clinical Practice (EFGCP).[36-38] All have stressed the need for evidence-based medicines for the increasingly older population. Medicines need to be appropriately investigated, with, if appropriate, specific efficacy and safety endpoints, where quality of life should outweigh longevity. To include the target population as much as possible, exclusion criteria should be fully justified – exclusion solely on the basis of age is not permissible. In addition, informed consent should be sought in all older people that are able to consent. If older subjects do not fully understand the nature, purpose and implications of participation in a clinical trial, their assent could be sought, in combination with the assent or consent of their legal or authorised representative.[37] In the current study, none of the included trials mentioned the assent procedure. Although this does not necessarily mean that such a procedure was not applied, it is encouraging that applying this procedure would result in more older and more vulnerable people being eligible for participation in clinical trials.

Other stakeholders should recognise their responsibilities, such as research ethics committees, especially because many clinical trial protocols submitted to university or hospital ethics

committees for approval use an upper age limit as exclusion criterion.[39] These committees might benefit from the inclusion of geriatric expertise. Medical journals could state that any exclusion criteria applied should be accompanied by justification of their use. Healthcare professionals involved in the selection of study participants should be aware of the need for older, representative subjects and limit the barriers to their participation. Patients and their carers or legal representatives need to be aware of the possibility to participate in clinical trials. An example of an initiative to improve this awareness is the website of the Clinical Research Network, which is part of the National Institute for Health Research in the United Kingdom.[40]

The EMA concluded that the ICH E7 guideline, together with the questions and answers document must be used more adequately, with a focus on the actual patient population.[36] This study suggests that guideline adherence is increasing in some sectors. The trials included in the current study were performed before the questions and answers document and EMA's geriatric medicines strategy were published. It will take time to implement the change in focus, such as the inclusion of participants aged ≥75 years and the representativeness of older people relative to the prevalence of the condition investigated in the target population.

Although the number of older participants randomised seems encouraging for some therapeutic indications, upper age limits are still frequently applied and exclusion criteria that more indirectly affect the inclusion of older people limit the inclusion of individuals from the target population. Since adequate information is essential for patients to receive appropriate drug therapy, it is crucial that medicines are evaluated in the older population. The PREDICT Charter clearly states: "Older people have the right to access evidence-based treatments."[38]

References

1. Fitzsimmons PR, Blayney S, Mina-Corkill S, Scott GO. Older participants are frequently excluded from Parkinson's disease research. *Parkinsonism Relat Disord* 2012; 18(5):585-9.
2. Mitchell SL, Sullivan EA, Lipsitz LA. Exclusion of elderly subjects from clinical trials for Parkinson disease. *Arch Neurol* 1997; 54(11):1393-8.
3. Dodd KS, Saczynski JS, Zhao Y, Goldberg RJ, Gurwitz JH. Exclusion of older adults and women from recent trials of acute coronary syndromes. *J Am Geriatr Soc* 2011; 59(3):506-11.
4. Foerch C, Czapowski D, Misselwitz B, Steinmetz H, Neumann-Haefelin T, Arbeitsgruppe Schlaganfall Hessen (ASH). Gender imbalances induced by age limits in stroke trials. *Neuroepidemiology* 2010; 35(3):226-30.
5. Green P, Maurer MS, Foody JM, Forman DE, Wenger NK. Representation of older adults in the late-breaking clinical trials American heart association 2011 scientific sessions. *J Am Coll Cardiol* 2012; 60(9):869-71.
6. Kitzman DW, Rich MW. Age disparities in heart failure research. *JAMA* 2010; 304(17):1950-1.
7. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011; 171(6):550-6.
8. Yonemori K, Hirakawa A, Komiyama N, Kouno T, Ando M, Fujiwara Y, et al. Participation of elderly patients in registration trials for oncology drug applications in Japan. *Ann Oncol* 2010; 21(10):2112-8.
9. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: A 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004; 22(22):4626-31.
10. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: Known problem, little progress. *J Clin Oncol* 2012; 30(17):2036-38.
11. Hutchins LF, Unger JM, Crowley JJ, Coltman Jr. CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999; 341(27):2061-7.
12. Clarfield AM, Friedman R. Survey of the age structure of "age-relevant" articles in four general medical journals. *J Am Geriatr Soc* 1985; 33(11):773-8.
13. Al-Refaie WB, Vickers SM, Zhong W, Parsons H, Rothenberger D, Habermann EB. Cancer trials versus the real world in the United States. *Ann Surg* 2011; 254(3):438-42.
14. Dowd R, Recker RR, Heaney RP. Study subjects and ordinary patients. *Osteoporos Int* 2000; 11(6):533-6.
15. Hori A, Shibata T, Kami M, Kusumi E, Narimatsu H, Kishi Y, et al. Age disparity between a cancer population and participants in clinical trials submitted as a new drug application of anticancer drugs in Japan. *Cancer* 2007; 109(12):2541-6.
16. Sharpe N. Clinical trials and the real world: selection bias and generalisability of trial results. *Cardiovasc Drugs Ther* 2002; 16(1):75-7.
17. Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry* 2002; 159(3):469-73.
18. Uijen AA, Bakx JC, Mokkink HG, van Weel C. Hypertension patients participating in trials differ in many aspects from patients treated in general practices. *J Clin Epidemiol* 2007; 60(4):330-5.
19. McMurdo M. Clinical research must include more older people. *BMJ* 2013; 346:f3899.
20. European Medicines Agency. Studies in support of special populations: geriatrics ICH E7 (CPMP/ICH/379/95). (Accessed November 25, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002875.pdf).

21. Committee for medicinal products for human use (CHMP). Adequacy of guidance on the elderly regarding medicinal products for human use. (Accessed November 25, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500049541.pdf).
22. Cherubini A, Del Signore S, Ouslander J, Semla T, Michel JP. Fighting against age discrimination in clinical trials. *J Am Geriatr Soc* 2010; 58(9):1791-6.
23. Cruz-Jentoft AJ, Carpena-Ruiz M, Montero-Errasquin B, Sanchez-Castellano C, Sanchez-Garcia E. Exclusion of older adults from ongoing clinical trials about type 2 diabetes mellitus. *J Am Geriatr Soc* 2013; 61(5):734-8.
24. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomised controlled trials published in high-impact general medical journals: A systematic sampling review. *JAMA* 2007; 297(11):1233-40.
25. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27(5):1047-53.
26. Website European Medicines Agency. European public assessment reports. (Accessed November 25, 2013, at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124).
27. World Health Organization. International clinical trials registry platform search portal. (Accessed November 25, 2013, at http://apps.who.int/trialsearch/Default.aspx).
28. U.S. National Institutes of Health. U.S. national institute of health clinical trials registry. (Accessed November 25, 2013, at http://www.clinicaltrials.gov/).
29. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2006; 354(8):821-31.
30. De Wulf M. Population pyramids of the world from 1950 to 2100. (Accessed November 25, 2013, at http://populationpyramid.net/).
31. Sander JW, Hart YM, Johnson AL, Shorvon SD. National general practice study of epilepsy: Newly diagnosed epileptic seizures in a general population. *Lancet* 1990; 336(8726):1267-71.
32. European Medicines Agency. Fablyn (lasofoxifene) – cessation of validity of the marketing authorisation in the European Union. (Accessed November 25, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2012/06/WC500129057.pdf).
33. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: A systematic review of the inclusion and analysis of older adults in randomised controlled trials. *J Gen Intern Med* 2011; 26(7):783-90.
34. Konrat C, Boutron I, Trinquart L, Auleley GR, Ricordeau P, Ravaud P. Underrepresentation of elderly people in randomised controlled trials. The example of trials of 4 widely prescribed drugs. *PLoS One* 2012; 7(3):e33559.
35. Leufkens HG, Urquhart J. Variability in patterns of drug usage. *J Pharm Pharmacol* 1994; 46 Suppl 1:433-7.
36. Europeans Medicines Agency. EMA geriatric medicines strategy. (Accessed November 25, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102291.pdf).
37. Diener L, Hugonot-Diener L, Alvino S, Baeyens JP, Bone MF, Chirita D, et al. Guidance synthesis. Medical research for and with older people in Europe: proposed ethical guidance for good clinical practice: ethical considerations. *J Nutr Health Aging* 2013; 17(7):625-7.
38. PREDICT Consortium. PREDICT charter for the rights of older people in clinical trials. (Accessed November 25, 2013, at http://www.predicteu.org/PREDICT_Charter/predict_charter.html).
39. Briggs R, Robinson S, O'Neill D. Ageism and clinical research. *Ir Med J* 2012; 105(9):311-2.
40. NIHR CRN CC. National institute for health research (NIHR) clinical research network website. (Accessed November 25, 2013, at http://www.crncc.nihr.ac.uk/ppi).

2.2

Information for adequate prescribing to older patients

An evaluation of the product information of 53 recently approved medicines

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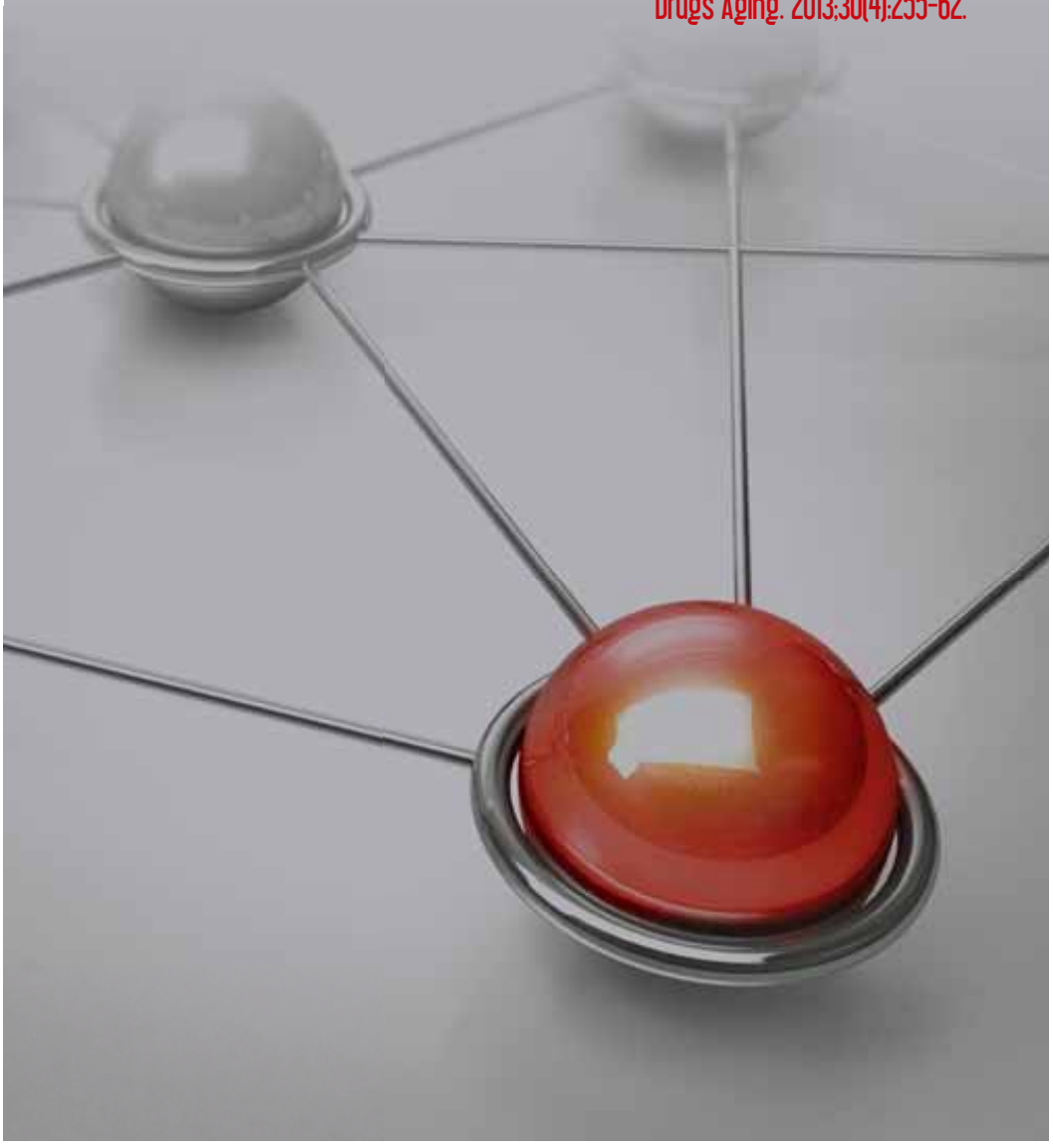


Abstract

Introduction Historically, older patients have been frequently excluded from clinical trials. This has a knock-on effect on the availability of relevant information from trials for healthcare professionals prescribing medicines to older individuals in daily clinical practice. The objective was to investigate the availability of information relevant to appropriate prescribing for older people in the summaries of product characteristics (SmPCs) of recently approved medicines.

Methods An analysis was undertaken of the SmPCs and European public assessment reports (EPARs) of all non-generic medicines indicated for diseases that are common in older individuals and that were approved by the European Medicines Agency between January 2008 and December 2010. The EPARs were considered the second most complete, publicly available document after the preauthorization dossier. The availability of information was evaluated for 19 items on the representation of and clinical experience in older people, as well as pharmacokinetic and drug–drug interaction studies. These items were derived from the ICH E7 guideline for studies involving geriatric populations in the SmPCs and EPARs. Information not included was classified as being essential or non-essential, based on the product characteristics.

Results Fifty-three medicines were investigated. Overall, information on the ICH E7 items was available in 56% of the SmPCs (EPARs 79%); 41% of the SmPCs (EPARs 24%) did not provide information that should have been included. Twenty-seven percent of the SmPCs, but 78% of the EPARs, provided information about the number of patients included. Moreover, 2% of the SmPCs (EPARs 51%) provided information about the exclusion of patients with common comorbidities, and 14% of the SmPCs, but 81% of the EPARs, provided information about exclusion based on age.

Conclusions SmPCs, unlike EPARs, do not sufficiently provide adequate information about older individuals. Consequently, it is not clear whether the information about efficacy and safety applies to the frail older patients often seen in daily practice. The SmPC is intended for use by healthcare professionals in daily clinical practice and provides basic information for safe and effective prescribing. As the EPAR describes regulatory considerations relevant to drug approval and is too long for daily use, the information about older individuals included in the SmPCs should be improved.

Introduction

Historically, people older than 65 years have been excluded from clinical trials conducted as part of the clinical development program of new medicinal products for ethical, methodological and practical reasons.[1–6] Since efficacy and safety data obtained in younger adults cannot always be extrapolated to older individuals, the evidence base for new medicines destined for use in older patients is weak.[2,7] This is particularly true for frail older patients and may hinder clinical decision-making.[8] It is recognised that the benefit/risk balance for some medicines may be disadvantageous in older people compared with younger people and can lead to drug-related hospital admissions or even death.[9–11]

These problems were recognised by the European and American regulatory agencies in the late 1980s.[2] In 1994, the regulatory authorities of Japan, the European Union and the US adopted the International Conference on Harmonization (ICH) guideline on geriatrics (E7) in order to obtain more evidence concerning the efficacy and safety of drugs in the clinical development program in older individuals.[12] The guideline focuses, from a regulatory point of view, on what investigations should be carried out in older people in the pre-authorisation phase and what information should be described in the application dossier of a new medicinal product. Although it is a guideline, a sponsor or pharmaceutical company has to give convincing reasons why it does not adhere to these recommendations. However, despite the introduction of the ICH E7 guideline, older individuals are still underrepresented in clinical trials.[3,8,13,14] In 2006, the European Medicines Agency (EMA) evaluated ten application dossiers of products for common indications in older individuals that had been approved for the European market between 2001 and 2006. It concluded that the ICH E7 recommendations were often only marginally fulfilled, even when the drugs concerned would be used to treat diseases characteristically associated with aging.[15]

That EMA study used information from the pre-authorisation dossier, which is accessible for regulatory authorities and the marketing authorisation holder only. In clinical practice, physicians and pharmacists only have access to the publicly available summaries of product characteristics (SmPCs) and the European public assessment reports (EPARs) in Europe and to the package insert (PI) in the US. The marketing authorisation holder is responsible for the content of the SmPC and PI, which is approved by the regulatory authorities. It contains the label (i.e., indication, dosing, warnings and other basic features of the medicine) and is intended as an information source for healthcare professionals for the effective and safe prescription of medicines.[16] The SmPC and PI often serve as the (sole) source of information for national prescribing guidelines and drug formularies. The EPAR explains regulatory considerations relevant to the scientific approval process by the European Commission and contains parts of the pre-authorisation dossier.[17] The Food and Drug Administration (FDA) does not provide a publicly available equivalent for the EPAR. Therefore, in this study the focus was on the SmPC and the EPAR. Since the SmPC is approved by the regulatory authorities and is intended for use by healthcare professionals in daily clinical practice, the aim of this study is to investigate the availability of information in SmPCs relevant to appropriate prescribing in older people, as recommended in the ICH E7 guideline.

Methods

Inclusion and exclusion criteria

All non-generic medicinal products that had been given marketing authorisation by the EMA between 1 January 2008 and 31 December 2010 were eligible if the SmPCs and EPARs were accessible via the EMA website. Only new chemical entities and complete and independent applications were eligible. The products had to be indicated either for diseases characteristically associated with aging (e.g., Alzheimer's disease) or for diseases frequently present in older individuals (e.g., diabetes mellitus, malignancies). Medicinal products not intended for use in older people were excluded, as were products for diseases not frequently or not associated with aging, provided that the researchers (EB, PAFJ, TCGE and HGML) were in agreement about this.

Data extraction

Data extraction was based on the ICH E7 guideline as summarised by the Committee for Medicinal Products for Human Use (CHMP) in 2006.[15] Topics mentioned in the ICH E7 guideline are: the definition of the population, clinical experience, pharmacokinetic studies, pharmacodynamic/dose response studies and drug–drug interaction studies. The CHMP summarised the guideline in 23 items. The item on whether the indication was within the scope of the ICH E7 guideline was eliminated, because this was an inclusion criterion of our study. Three items on the types of pharmacokinetic studies were combined, and one item had already been described in other items, i.e., "Do the geriatrics constitute a major proportion in the clinical database?" As a result, 19 items remained. For the purposes of this study, these items were rephrased into questions on whether information on older people was available in the SmPCs and EPARs (table 1).

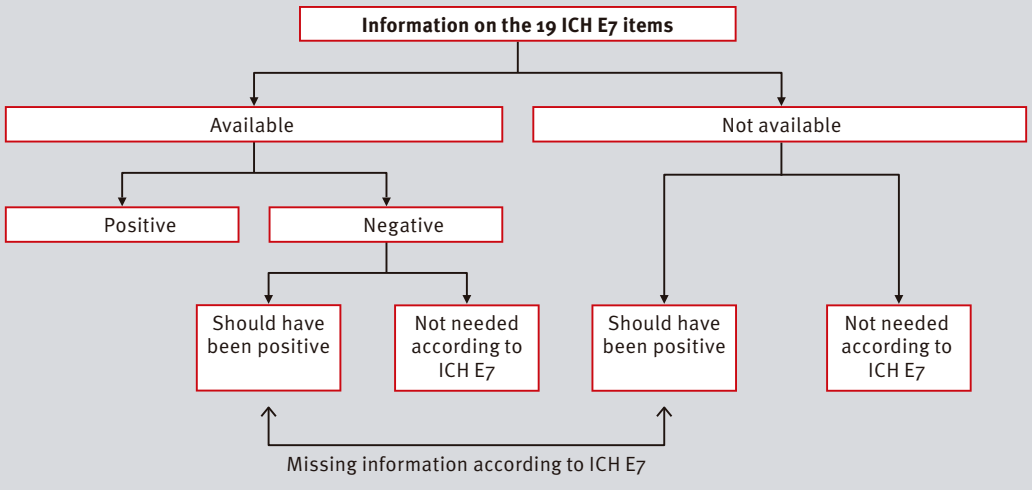
The answers to the 19 questions were classified as 'available' and 'non-available' (figure 1). Available information was further divided into positive and negative information. For example, the statement that people older than 75 years were excluded from a study was considered available, but negative information. Negative information and non-available information were divided into information that was relevant or not relevant, depending on the characteristics of the medicine investigated.[12] For example, the statement that drug–drug interactions had not been studied was considered available, negative information. If the drug concerned was a systemically acting agent metabolised by liver enzymes, the ICH E7 guideline states that drug–drug interaction studies should be performed, and thus this information was relevant and should have been provided. This information is not necessary for a locally acting medicinal product. The approval date, the administration route and the therapeutic indication as stated at the EMA website and in the SmPCs were also recorded.[12]

TABLE 1 The items extracted from the ICH E7 guideline[12,15]

Category	Item
Nature of the studied population	Is it clear whether participants ≥65 years have been included?
	Is it clear whether participants ≥75 years have been included?
	Is it clear whether there are exclusions based on age?
	Is it clear whether there are exclusions based on common co-morbidity in people ≥65y?
Clinical experience in older persons	Is there information on the number of participants ≥65 years?
	Is there an evaluation for age-related differences in efficacy?
	Is there an evaluation for age-related differences in dose response?
	Is there an evaluation for age-related differences in adverse events?
Pharmacokinetic studies	Is it clear that the drug has a normal or special PK behaviour?
	Is there information on what type of PK study has been performed in older persons?
	Is there an evaluation of demographic factors?
	Is there an evaluation of physiological factors?
	Is there information on the extent of renal excretion of active substance?
	Is there information on the extent of hepatic excretion of active substance?
	Is there information on studies in renally impaired patients?
	Is there information on studies in hepatically impaired patients?
Drug–drug interaction studies	Is there information on the therapeutic range?
	Is there information on absence or presence of a relevant CYP450 metabolism?
	Is it clear whether drug–drug interaction studies have been performed?

PK pharmacokinetic, CYP450 cytochrome P450 enzyme system

FIGURE 1 Subdivision of available and missing information



Data analysis methods

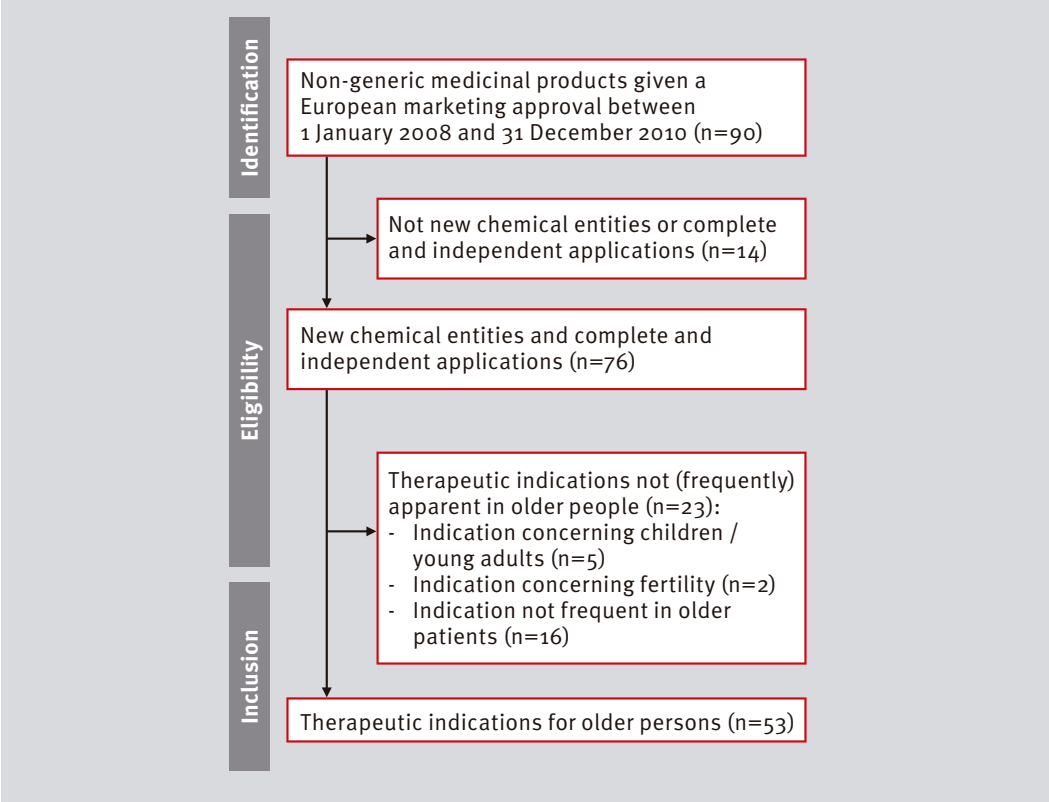
A stratified analysis was performed. First, the site of action, i.e., systemic or local, was analysed, because pharmacokinetics and drug–drug interactions do not need to be studied for locally acting medicinal products. Second, new chemical entities were evaluated, because these are the first representatives of a new pharmacological mechanism of action. Third, the year of approval was recorded.

The results are presented as percentage frequencies. Descriptive statistical analysis was performed with SPSS version 18.0 (IBM SPSS Inc., Chicago, IL, USA).

Results

Between 1 January 2008 and 31 December 2010, 90 non-generic medicinal products received European marketing authorisation (figure 2). Most of them were new chemical entities or complete and independent applications. Of these, 53 medicinal products were included in the current study (table 2; drug names in the supplementary table).

FIGURE 2 Dossier identification, selection and inclusion



Considering the availability of information about the ICH E7 items, overall, 56% was provided in the SmPCs; 50% concerned positive information (EPARs 79 and 69%, respectively). Forty-one percent of the relevant items was lacking in the SmPCs (EPARs 24%).

Figure 3a shows the positive information given in the SmPCs and EPARs. This information is relevant to appropriate prescribing in older people. Overall, 60% (range 23–70%) of the required information about pharmacokinetic studies as well as 67% of the information about drug–drug interaction studies was present in the SmPCs, which is addressed in specific guidelines next to the ICH E7 guideline. Information solely recommended in this guideline, i.e., about the population studied and clinical experience in older people, was reported in 24 and 43% of the SmPCs, respectively (EPARs 62 and 66%, respectively).

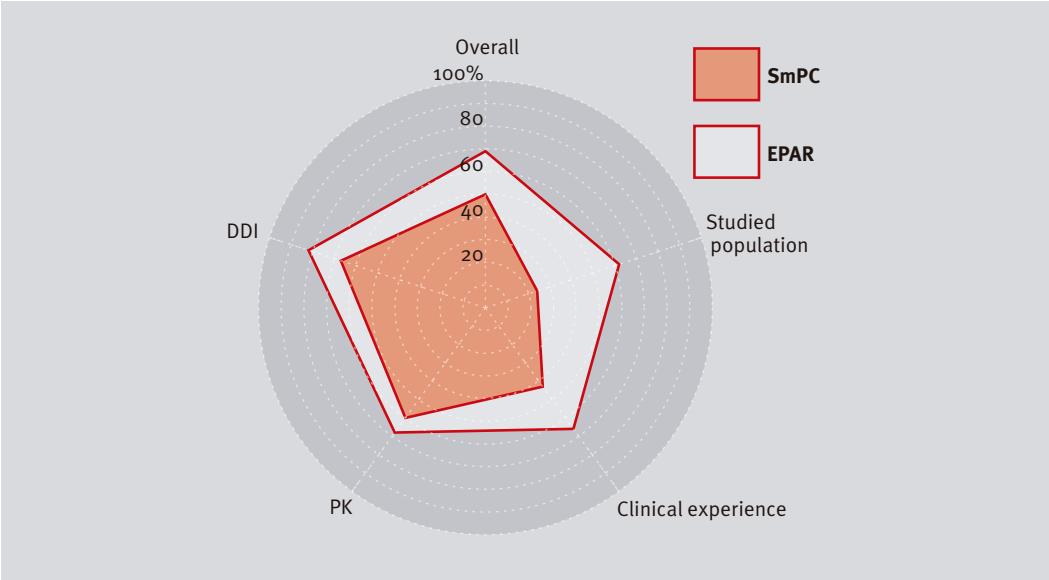
When focusing on the category that was least provided in the SmPCs and EPARs, i.e., the definition of the population, almost 50% of the SmPCs stated that participants older than 65 and/or 75 years had been included (figure 3b), 14% stated that age was an exclusion criterion (8% gave the age cut-off and 6% did not), and 2% stated that older individuals had been excluded because of common comorbidities. Twenty-three percent of the SmPCs provided information about pharmacokinetic studies in older people.

TABLE 2 Characteristics of the included medicinal products

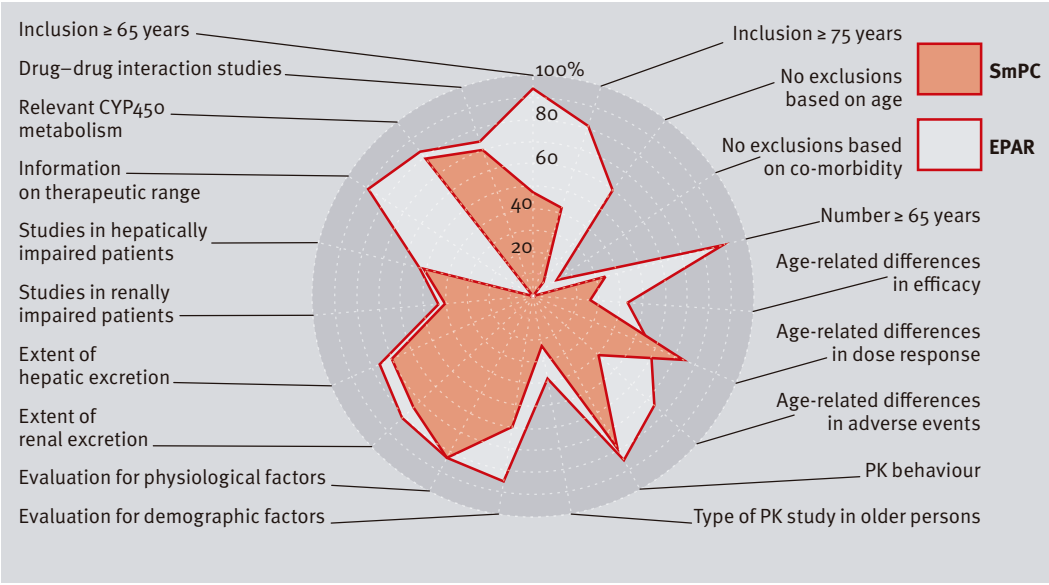
Characteristics	No (%) (n=53)
Pharmacodynamic effect	
Systemic	48 (91)
Local	5 (9)
New chemical entities	
New chemical entities	21 (40)
Complete and independent applications	32 (60)
Year of approval	
2008	19 (36)
2009	25 (47)
2010	9 (17)
Therapeutic area	
Neoplasms	12 (23)
Diseases of the musculoskeletal system and connective tissue	10 (19)
Diseases of the circulatory system	8 (15)
Endocrine, nutritional and metabolic diseases	5 (9)
Infectious diseases	5 (9)
Other therapeutic areas	13 (25)

FIGURE 3 Representation of the percentage of available and studied information in the SmPCs and EPARs

a Per category



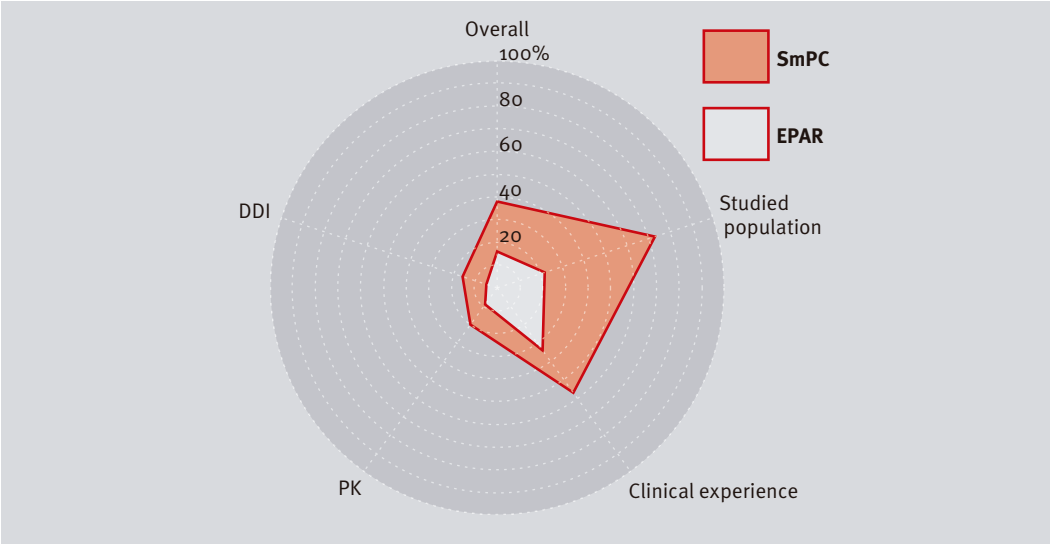
b Per item



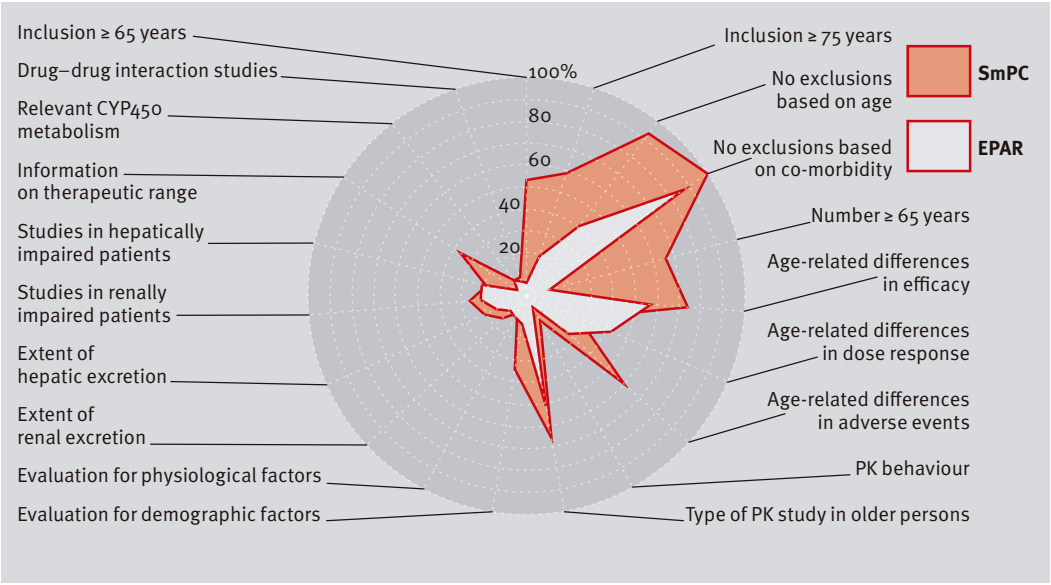
PK pharmacokinetic studies, DDI drug–drug interaction studies

FIGURE 4 Representation of the percentage of non-available information that should have been positive in the SmPCs and EPARs

a Per category



b Per item



The higher the percentage value, the greater the amount of information that was missing. PK pharmacokinetic studies, DDI drug–drug interaction studies

Figure 4a gives an overview of information that should have been reported. The higher the percentage, the more relevant information was missing. Overall, 38% of the required information was missing in the SmPCs (EPAR 16%): in the SmPCs most information was lacking on the definition of the studied population (73%; EPARs 22%) and the clinical experience in older persons (57%; EPARs 34%). All SmPCs and 87% of the EPARs failed to report relevant information about exclusions based on common comorbidities; 86 and 40%, respectively, failed to provide information about exclusions based on an upper age cut-off; 74 and 57%, respectively, did not mention an evaluation for age-related differences in efficacy; 60 and 26%, respectively, did not provide information about an evaluation for adverse events.

The stratified analysis showed that the SmPCs provided less information about locally acting medicinal products than they did about systemically acting medicines. The frequency of missing data was comparable. In total, 41% of the SmPCs of new chemical entities reported relevant information at marketing approval compared with 50% for the overall group. Of the medicines approved for the European market in 2008, the SmPCs provided more positive information (54%) than for medicines approved in 2009 and 2010 (47 and 48%, respectively).

Discussion

This is the first published study to investigate the availability of information necessary for appropriate prescribing in older people in the SmPCs of recently approved medicinal products. The overall results indicate that, in the SmPCs, information on the ICH E7 recommendations is incomplete, with a positive availability of 50%. This is remarkable, since the information is present in the EPARs, which cover 69% of the ICH E7 items. In most cases healthcare professionals cannot find information about the study population, since common comorbidities in older individuals were mentioned as an exclusion criterion for clinical development programs in only 2% of the SmPCs and an upper cut-off for age as an exclusion criterion in 14%. Moreover, less than 40% of the SmPCs mentioned that age-related differences in efficacy and safety had been evaluated. Consequently, it is not clear whether the information about efficacy and safety applies to the frail older patients often seen in daily practice, which appears to contradict the function of an SmPC as an "information source for healthcare professionals for the safe and effective prescribing of medicines".[16] In contrast, the EPARs provided more information about these aspects, but as these documents are long (about 40–80 pages), they are not suitable for use in daily medical practice.

The SmPCs provided more information about pharmacokinetics and drug–drug interaction studies than about the definition of older populations and the clinical experience with these individuals. Recommendations for pharmacokinetic and drug–drug interaction studies are extensively described in other guidelines, as well as for patients with impaired renal function or impaired hepatic function.[18–21] Even so, there was little information about the items solely described in the ICH E7 guideline. This seems to be contradictory to the EMA's statement that "the Agency will undertake specific efforts to ensure that the needs of older people are taken into account in the development and evaluation of new medicines".[22] In July 2010, the

EMA again promoted the optimal implementation of existing regulations and guidelines, including a review of the ICH E7 guideline.[23]

Previous research on geriatric information in the situation in the US focused on the package inserts (PIs) of commonly prescribed drugs in older people. It was found that, in general, information about drug use in older people was present in 82% (41/50) of investigated PIs.[24] Although around 50% of the PIs provided precautions for older people, most did not give any specifications on problems that might be faced. As in the current study, information about dosing instructions, for example, simply was not available, thereby leaving the healthcare professional in doubt about whether dosing adjustments might be needed.

In the current study, no assumptions were made about missing information. The CHMP study evaluated ten marketing authorisation application dossiers of products for indications common in older people.[15] The number of patients older than 65 or 75 years was calculated assuming that the age distribution of the trial population showed a Gaussian distribution. Since older individuals are frequently excluded from clinical trials[1–4,6,8,13,14], this assumption could have led to an overoptimistic impression of adherence to the ICH E7 guideline. The CHMP concluded that the adherence to the guideline was reasonable, even though specific recommendations were often marginally met. This was also the case for drugs used in diseases characteristically associated with aging.[15] The CHMP study concentrated on pre-authorisation dossiers, whereas the current study considered EPARs and SmPCs, which probably contain less information than pre-authorisation dossiers.

It should be noted that the ICH E7 guideline was developed by regulators and the pharmaceutical industry. The primary focus of the current study was the availability of information needed by healthcare professionals in daily clinical practice. This study did not address which aspects of the ICH E7 guideline are relevant to healthcare professionals in order to promote appropriate prescribing to frail older patients. This is something currently being investigated by the authors. It might also be appropriate to assess whether the pharmaceutical industry adheres to the ICH E7 guideline by evaluating the pre-authorisation dossiers of the investigated products.

The SmPC is considered "the basis of information for healthcare professionals on how to use the medicinal product safely and effectively," as stated in the guideline on summary of product characteristics.[16] Although it is recommended that the text should be clear and concise, there are no instructions regarding the word count. In the current digital era, information on older people should be easy to find in a digital document. Our findings show, in accordance with the above-mentioned American PI study[24], that in many cases the SmPC fails to provide sufficient information to allow healthcare professionals to prescribe appropriately in the older population. Healthcare professionals need information from the performed trials[25], such as the characteristics of the population studied. This means that information about the number of participants aged older than 65 years and, especially, 75 years should be included, as well as whether patients were excluded based on the basis of an upper age cut-off. Also, it should be clear what (common) comorbidities were reasons for exclusion. Furthermore, a clear evaluation of age-related differences in efficacy and safety, and of the results of pharmacokinetic

studies in older individuals, especially those older than 75 years, is necessary to enable healthcare professionals to make informed prescribing decisions.

In conclusion, SmPCs, unlike EPARs, do not sufficiently provide adequate information about older people. As a result, it remains unclear whether the information about efficacy and safety applies to the frail older population in daily practice. The evidence base for appropriate prescribing in older individuals is fairly well represented in the EPARs. However, this document describes the regulatory considerations relevant to drug approval and is too long for daily use. Since the SmPC is specifically intended for use by healthcare professionals in daily clinical practice, it should include the evidence-based information to support appropriate prescribing to older patients.

References

1. Bartlett C, Davey P, Dieppe P, Doyal L, Ebrahim S, Egger M. Women, older persons, and ethnic minorities: factors associated with their inclusion in randomised trials of statins 1990 to 2001. *Heart* 2003; 89(3):327-8.
2. Cherubini A, Del Signore S, Ouslander J, Semla T, Michel JP. Fighting against age discrimination in clinical trials. *J Am Geriatr Soc* 2010; 58(9):1791-6.
3. Dodd KS, Saczynski JS, Zhao Y, Goldberg RJ, Gurwitz JH. Exclusion of older adults and women from recent trials of acute coronary syndromes. *J Am Geriatr Soc* 2011; 59(3):506-11.
4. McMurdo ME, Witham MD, Gillespie ND. Including older people in clinical research. *BMJ* 2005; 331(7524):1036-7.
5. McMurdo ME, Roberts H, Parker S, Wyatt N, May H, Goodman C, et al. Improving recruitment of older people to research through good practice. *Age Ageing* 2011; 40(6):659-65.
6. Witham MD, McMurdo ME. How to get older people included in clinical studies. *Drugs Aging* 2007; 24(3):187-96.
7. Limb M. Excluding older patients from trials is "bad science", conference hears. *BMJ* 2011; 29(343):d6305.
8. Cho S, Lau SWJ, Tandon V, et al. Geriatric drug evaluation: where are we now and where should we be in the future? *Arch Intern Med* 2011; 171(10):937–40.
9. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med* 2008; 168(17):1890-6.
10. Carrasco-Garrido P, de Andres LA, Barrera VH, de Miguel GA, Jimenez-Garcia R. Trends of adverse drug reactions related-hospitalizations in Spain (2001-2006). *BMC Health Serv Res* 2010; 10:287.
11. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; 329(7456):15-9.
12. European Medicines Agency. Studies in support of special populations: geriatrics ICH E7 (CPMP/ICH/379/95). (Accessed December 17, 2012, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002875.pdf).
13. Hutchins LF, Unger JM, Crowley JJ, Coltman Jr. CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999; 341(27):2061-7.
14. Giron MS, Fastbom J, Winblad B. Clinical trials of potential antidepressants: to what extent are the elderly represented: a review. *Int J Geriatr Psychiatry* 2005; 20(3):201–17.
15. Committee for medicinal products for human use (CHMP). Adequacy of guidance on the elderly regarding medicinal products for human use. (Accessed December 17, 2012, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500049541.pdf).
16. European Commission. A guideline on summary of product characteristics. (Accessed December 17, 2012, at http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf).
17. Website European Medicines Agency. European public assessment reports. (Accessed December 17, 2012, at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124).
18. Committee for medicinal products for human use (CHMP). Guideline on investigation of drug interactions—draft. (Accessed December 17, 2012, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/05/WC500090112.pdf).

19. Committee for medicinal products for human use (CHMP). Guideline on evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. (Accessed December 17, 2012, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003122.pdf).

20. Committee for medicinal products for human use (CHMP). Guideline on evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function. (Accessed December 17, 2012, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003123.pdf).

21. Committee for medicinal products for human use (CHMP). Guideline on pharmacokinetic studies in man. (Accessed December 17, 2012, at http:// www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003127.pdf).

22. Committee for medicinal products for human use (CHMP). EMA geriatric medicines strategy. (Accessed December 17, 2012, at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102291.pdf).

23. Committee for medicinal products for human use (CHMP). ICH topic E7 studies in support of special populations: geriatrics; questions and answers. (Accessed December 17, 2012, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500005218.pdf).

24. Steinmetz KL, Coley KC, Pollock BG. Assessment of geriatric information on the drug label for commonly prescribed drugs in older people. *J Am Geriatr Soc* 2005; 53(5):891-4.

25. Witham MD. Drug trials and older people: time to embrace the complexity of age. *Drugs Aging* 2011; 28(8):679–80.

2.3

Availability and clinical applicability of information for rational prescribing to older patients in European and US drug compendia

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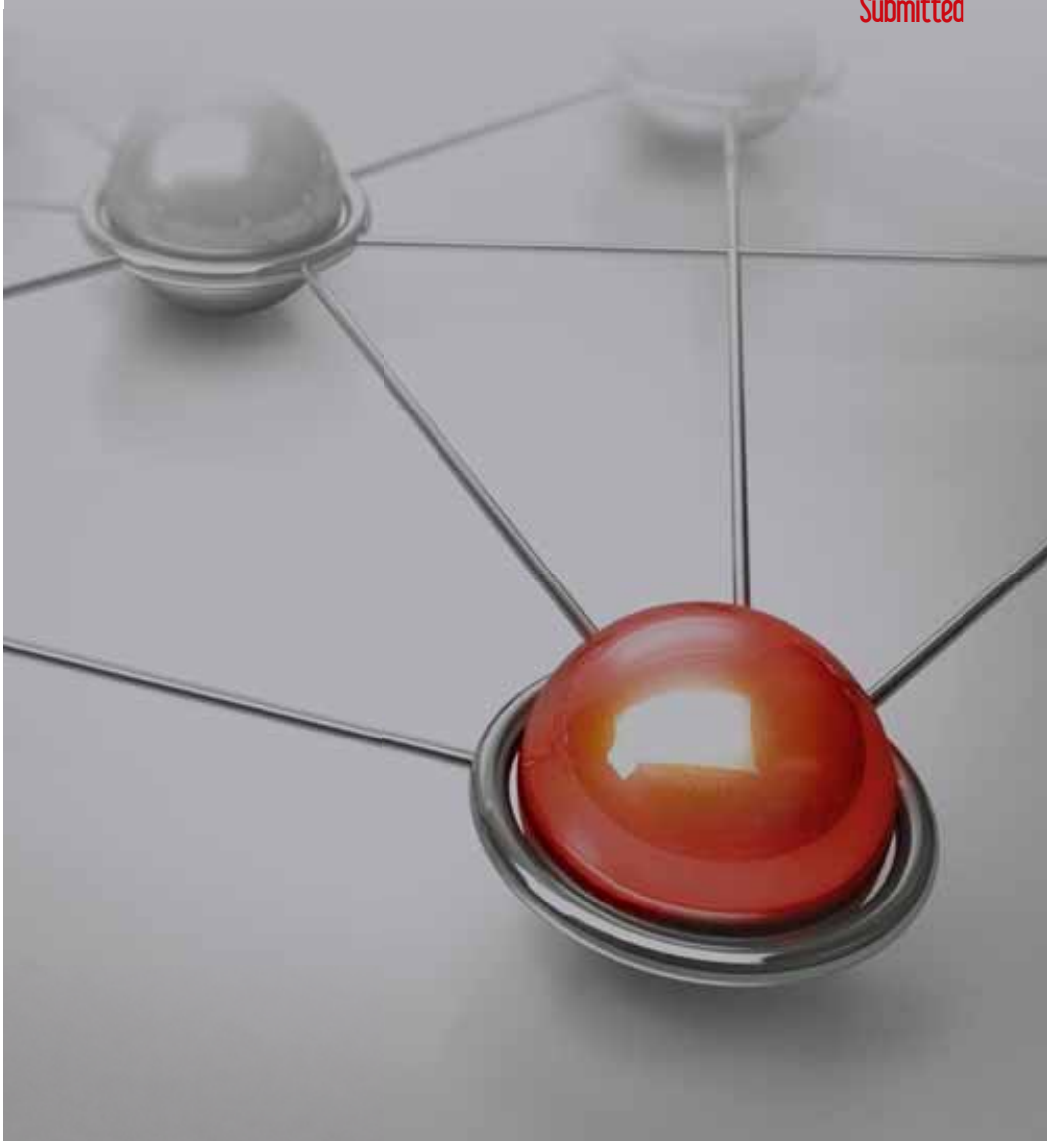
Submitted



Abstract

Introduction Healthcare professionals in daily practice can use drug compendia as source of information for the rational prescribing of medicines. This study investigated the availability and clinical applicability of information about older people in European and US compendia.

Methods The information provided about 35 medicines in the Belgian Repertorium, German Rote Liste, British National Formulary, Dutch Farmacotherapeutisch Kompas, and US Physician's Desk Reference (PDR, containing the Concise Monograph and the Product Label) was investigated. The medicines were indicated for diseases common in older people, had a first European centralised approval between 2008 and 2011 and an FDA approval before October 2012. A 19-item checklist, based on the legislative ICH E7 guideline, was used to investigate the availability and, if relevant, clinical applicability of information on the studied population, clinical experience, pharmacokinetic properties and drug–drug interactions. Descriptive statistics were used.

Results Overall, 19% of information relevant to prescribing to older patients was available and applicable. The Belgian Repertorium provided the least information (7%), the PDR the most (47%). Information about the nature of the studied population was provided least frequently (14%) and information about drug–drug interactions most frequently (49%). Most available information was applicable, except for information about age-related differences in adverse effects and the need for monitoring in renal impairment.

Conclusions Current European compendia, and to a lesser extent the PDR, do not provide sufficient clinically relevant information about medicines frequently prescribed to older patients. As these compendia are widely used to guide prescribing, the information about older individuals should be improved.

Introduction

Healthcare professionals often refer to drug compendia to gain information for the selection and clinical use of medicines in older patients. This information comes from the official product information, the European summary of product characteristics (SmPC) and the US product label (PL), supplemented with information from other sources.[1-5] In turn, the SmPC and PL are based on the pre-authorisation dossier, which includes the chemical, pharmacologic and toxicity characteristics of the medicine and reports of the animal and human studies performed, such as clinical trials investigating the efficacy and safety of the medicine.[6] In order to improve the inclusion of older individuals in clinical trials, the International Conference on Harmonization guideline for studies in support of geriatric populations (ICH E7) was adopted in 1994 by the regulatory authorities of Europe, the USA, and Japan.[7] This guideline describes how many and what proportion of older subjects should be included in clinical trials and what information should be made available when a new drug is approved. In a recent study of the availability of information to support rational prescribing to older patients, half of the items mentioned in the ICH E7 guideline appeared to be reflected in the SmPCs.[8] A comparable assessment of medicines commonly used by older patients showed that relevant information was provided by 82% of the PLs.[9] Although this seems a satisfactorily high proportion, only about 50% of the PLs contained warnings and only 56% gave specific dosing information for older patients. Thus, although information is available, not all of it is clinically applicable.

Therefore, this study aims to investigate the availability and clinical applicability of information relevant to rational prescribing to older patients in the national drug compendia of European countries and the USA.

Methods

Selection of drug compendia

This study was based on the ICH E7 guideline.[10] Therefore, drug compendia of the USA, Japan, and the European countries included in the confederacy of the European Union in 1994 were eligible for inclusion, if they were available in English, German, or Dutch. As a result, the compendia of Belgium, Germany, Ireland, the Netherlands, the United Kingdom and the USA were included.

In these countries, geriatricians, general practitioners and pharmacists affiliated to relevant societies were asked (see Acknowledgements), by email, which compendia health professionals use when prescribing. At least three responses per country were obtained, and if the answers were consistent, that compendium was included. If the responses were inconclusive, the investigators decided which compendium was included, based on the current literature. Consequently, the Belgian *Repertorium* and *Folia* (further mentioned as Repertorium),[1] the German *Rote Liste* (RL),[4] the Dutch *Farmacotherapeutisch Kompas* (FK),[2] the British National Formulary (BNF)[11] – used in the United Kingdom and in Ireland – and the US

Physician's Desk Reference (PDR), which includes the Concise Monograph (CM) and the Product Label (PL), were included.[5]

Selection of medicines

All non-generic medicines that were approved by the EMA between 1 January 2008 and 1 January 2011 and approved by the FDA before 1 October 2012 and which are indicated for diseases highly prevalent in older individuals were included.

Outcomes

Availability of information

The ICH E7 guideline, as summarised by the Committee for Medicinal Products for Human Use in 2006 and used in a previous study, was adapted for the current study.[8,12] Four topics, the nature of the studied population, clinical experience in older people, pharmacokinetic studies, and drug–drug interaction studies, contained 19 items. These items were rephrased into questions on whether information about older people was available in the compendia (table 1). The answers were classified as 'available' and 'non-available' (figure 1). Available information was further classified as positive or negative information. For example, information about patients aged ≥65 years investigated in clinical trials was considered positive information; information that the medicine had not been investigated in older patients was considered available, negative information. Statements such as "experience in older patients is limited" were considered unclear. Not available, unclear, or negative information was classified as information that could have been positive, or as not needed, depending on the characteristics of the medicine investigated. For example, the extent of renal clearance was considered not necessary for locally acting medication.

Clinical applicability

The clinical applicability of 13 items was evaluated by predetermined criteria (table 1, supplementary table 2). Applicable information included specific warnings or instructions for prescribers, e.g. "the dose should be halved for patients over 75 years". For the items about patients with renal or hepatic impairment, the Systematic Information for Monitoring

FIGURE 1 Subdivision of available and non-available information

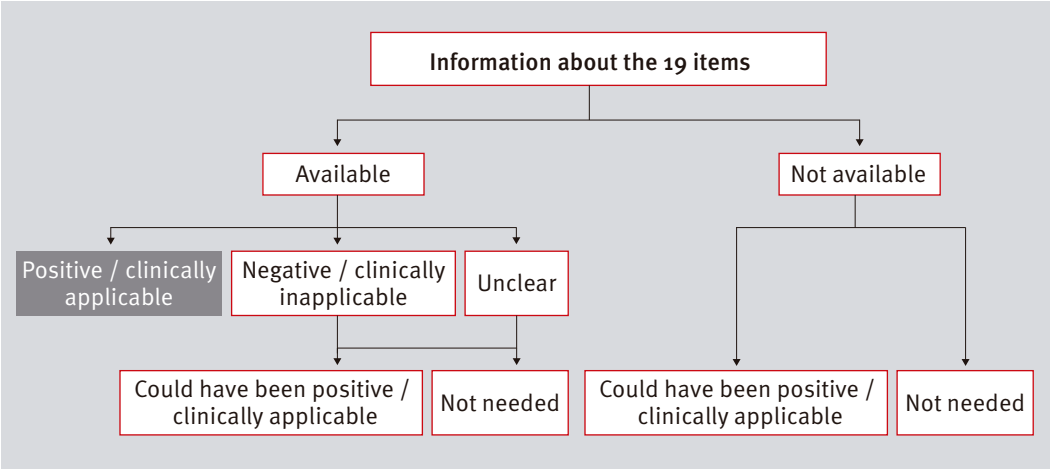


TABLE 1 The 19-item checklist

Items	Availability of information	Clinical applicability
Nature of the studied population		
Is information available about investigated participants ≥65 years?	+	N/A
Is information available about investigated participants ≥75 years?	+	N/A
Is information available about an upper age cut-off?	+	N/A
Is information available about exclusions based on comorbidity probably present in people ≥65 years?	+	N/A
Clinical experience in older people		
Is information available about the number of participants ≥65 years?	+	N/A
Is information available about age-related differences in efficacy?	+	+
Is information available about age-related differences in dose response?	+	+
Is information available about age-related differences in adverse events?	+	+
Pharmacokinetic properties		
Is information available about the PK behaviour of the drug?	+	N/A
Is information available about the PK behaviour in older people?	+	+
Is information available about the influence of demographic factors on the PK?	+	+
Is information available about the influence of physiological factors on the PK?	+	+
Is information available about the extent of renal excretion of active substance?	+	+
Is information available about the extent of hepatic excretion of active substance?	+	+
Is information available about renally impaired patients?	+	+
Is information available about hepatically impaired patients?	+	+
Drug–drug interactions		
Is information available about the therapeutic range?	+	+
Is information available about absence or presence of a relevant CYP450 metabolism?	+	+
Is information available about drug–drug interactions?	+	+

CYP450 cytochrome P450 enzyme system; PK pharmacokinetic

(SIM) score was used.[13] This score evaluates the presence of information on seven criteria: 'why monitor', 'what to monitor', 'when to start monitoring', 'when to stop monitoring', 'how frequently monitor', 'critical value', and 'how to respond'. The information was considered clinically applicable if at least the items 'what to monitor', 'critical value', and 'how to respond' were described. Mention that renal or hepatic function should be assessed was considered applicable information about 'what to monitor'.

Data analysis

The characteristics of the compendia are presented in a descriptive way; the availability and applicability of the information are presented as frequencies (%). The statistical analyses were performed with SPSS version 20.0 (IBM SPSS Inc., Chicago, IL, USA). Medication that was not included in a compendium was excluded from the data analysis of that compendium.

All data were collected and classified by one investigator (JLB), and validated in a sample of 17% of the medicines in each compendium by a second investigator (EB). In more than 97% of the sample, both investigators agreed directly. Consensus was reached in the classification of the remaining items.

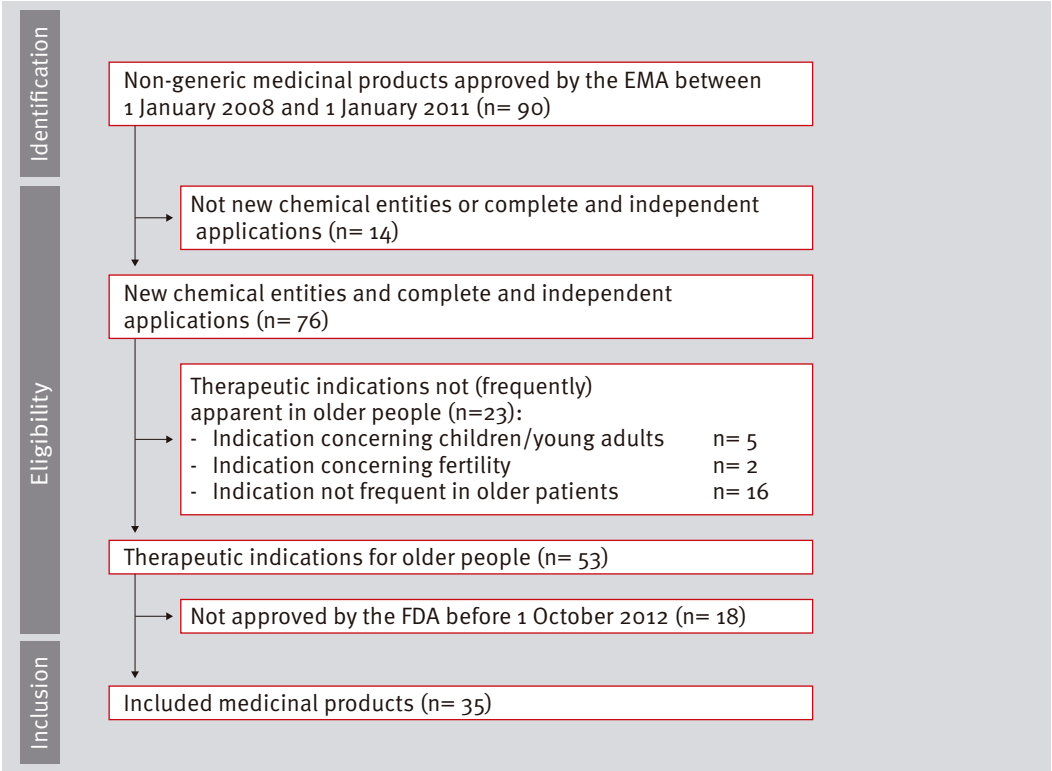
Results

Characteristics of the drug compendia

Unlike the other compendia, the PDR contained two information sources: the CM and the PL. The latter included 7 to 32 print pages and provided a summary at the top of each label. The other compendia enclosed approximately two print pages. The Repertorium mainly provided information about therapeutic groups, e.g., antipsychotics, than about individual products. In the German RL, the text was written in abbreviations.

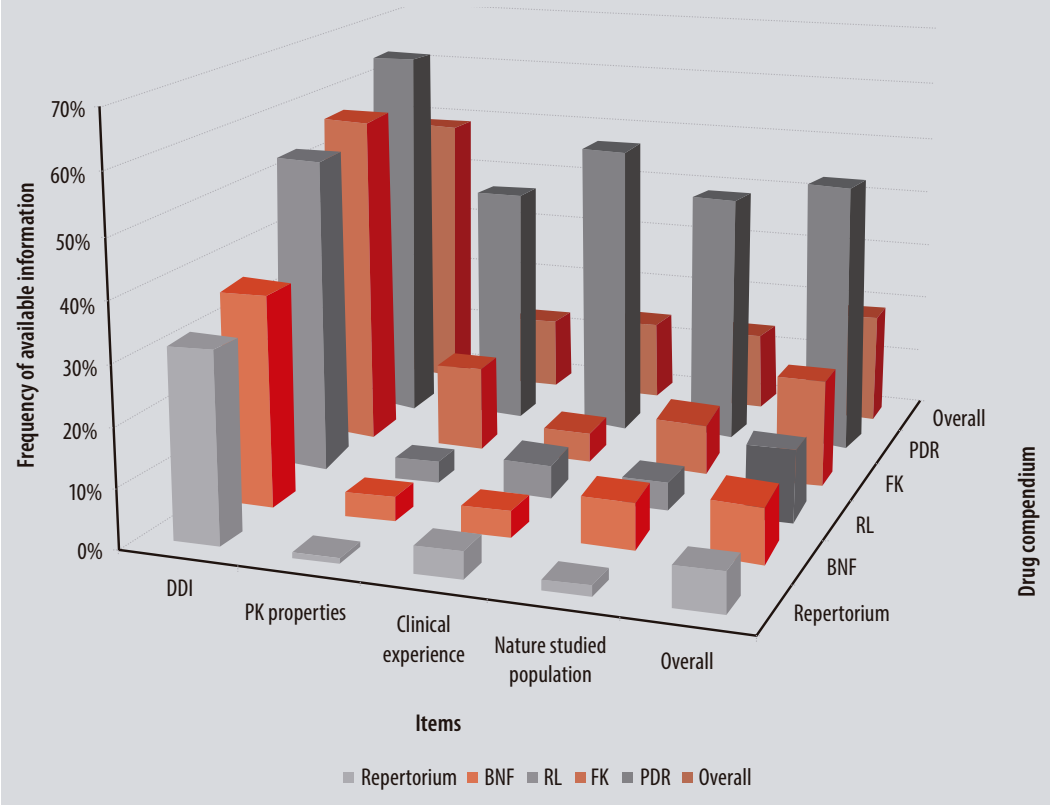
In all compendia, subheadings were used, such as 'indications', 'adverse reactions', and 'dosage'. In addition to these headings, the BNF and the PL included subheadings for renal and hepatic impairment. In comparison, the FK, the RL, and the CM provided such information in the precautions and warnings section. The PL was the sole source that contained a section about the use of drugs in geriatric patients.

FIGURE 2 The inclusion of the medicinal products



EMA European Medicines Agency; FDA US Food and Drug Administration

FIGURE 3 The proportion of available and applicable information per category



Shown are the percentages of available and applicable information in the five drug compendia per information category, as well as overall frequencies. PDR Physician's Desk Reference – US; FK *Farmacotherapeutisch Kompas* – the Netherlands; RL *Rote Liste* – Germany; BNF British National Formulary – UK, Ireland; *Repertorium* – Belgium; PK pharmacokinetic; DDI drug–drug interaction

Characteristics of the medicines

Thirty-five medicines met the inclusion criteria (figure 2). Most medicines were registered for the treatment of neoplasms (n=8; 23%), diseases of the musculoskeletal system and connective tissue (n=6; 16%), diseases of the circulatory system, and endocrine, nutritional and metabolic diseases (both n=4; 11%). Supplementary table 1 shows the drug names and therapeutic indications. Of these medicines, 27 were present in the Belgian Repertorium, 32 in the Dutch FK, 33 in the BNF, 34 in the German RL and 34 in the PDR (34 in the CM and 21 in the PL).

Availability of information

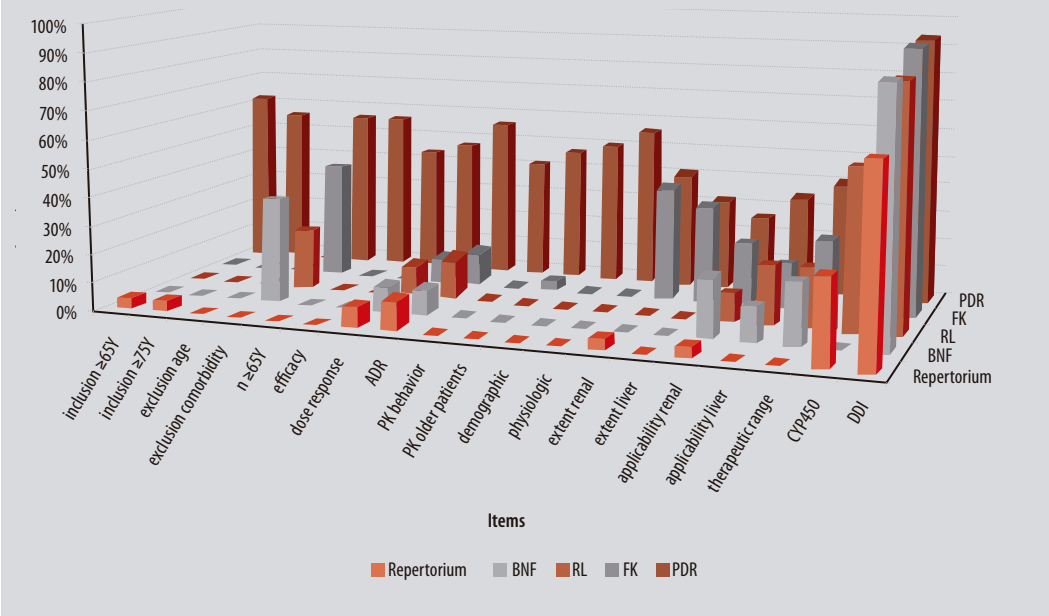
On the basis of the 19 items, for all selected medicines included in the five compendia, overall, 19% of the information was available and applicable, ranging from 7% in the Repertorium to 47% in the PDR (figure 3).

Nature of the studied population

Overall, 14% of the information about the nature of the studied population (4 items) was available in the five compendia, ranging from 2% in the Repertorium to 43% in the PDR (figure 3). Whether people aged 65 and 75 years or older had been included in clinical trials

was mentioned for 4% of medicines in the Repertorium, but in none of the other European compendia, and in 62% and 56% of the medicines included in the PDR, respectively (figure 4). None of the compendia mentioned whether upper age exclusion criteria had been used in clinical trials.

FIGURE 4 **The proportion of available and applicable information per item**



Shown are the percentages of available and applicable information in the five drug compendia depicted for all 19 items. PDR Physician's Desk Reference – US; FK *Farmacotherapeutisch Kompas* – the Netherlands; RL *Rote Liste* – Germany; BNF British National Formulary – UK, Ireland; *Repertorium* – Belgium. ADR adverse drug reaction; PK pharmacokinetic; CYP450 Cytochrome P450; DDI drug–drug interaction

Clinical experience in older people

Information about clinical experience in older people (4 items) was available and applicable for 14% of the medicines included in the compendia (range 5% [Repertorium, BNF, FK]–51% [PDR]) (figure 3). The number of older patients investigated in clinical trials was not reported in the European compendia; it was reported for 56% of the medicines included in the PDR (figure 4). The European compendia did not mention whether age-related differences in medicine efficacy had been investigated, but such information was provided for 44% of the medicines included in the PDR. Age-related differences in adverse drug reactions and in dose response were described for 9–15% and 7–12% of the medicines included in the European compendia, respectively; the PDR mentioned these differences for 47% and 56% of included medicines, respectively.

Pharmacokinetic properties

Pharmacokinetic properties (8 items) were mentioned for 13% of the included medicines; most frequently in the PDR (41%) and the Dutch FK (14%), but for 1–4% of the medicines in the other compendia (figure 3). Information about the extent of renal and hepatic excretion and about the actions needed in renally and hepatically impaired patients was most frequently available (figure 4). None of the European compendia provided information about

the effect of weight, ethnicity, and comorbidities on pharmacokinetic parameters of a given medicine; the PDR mentioned those demographic and physiologic parameters for 50% and 56% of medicines, respectively.

Drug–drug interactions

Information about the category of drug–drug interactions (3 items) was available for 49% of the medicines (range 32% [Repertorium]–65% [PDR]) (figure 3). Information about the therapeutic range of a medicine, such as a description of a maximum dose, was not included in the Repertorium, but was for 21–25% of medicines included in the other European compendia, and for 41% of the medicines included in the PDR (figure 4). A list of relevant drug–drug interactions was most frequently available (range 67% [Repertorium]–94% [PDR]).

Clinical applicability of information

For the majority of medicines, the information provided in the compendia was applicable, except for, firstly, information about age-related differences in adverse drug reactions. In the Repertorium and the PL, available information was also applicable; in the RL and the BNF, information was available for 26% of the medicines, but applicable for 14% and 9%, respectively. The greatest difference between availability and applicability of information was seen in the CM: information was available for 37% of the medicines, but was applicable for 14%. Secondly, the clinical applicability of information about renally impaired patients varied for medicines that were excreted renally in clinically relevant degrees (n=16). The PDR, the Dutch FK and the BNF provided applicable information about at least 'what to monitor', a 'critical value' and 'how to respond' for about half of the medicines investigated (56%, 54% and 47%, respectively). The Belgian Repertorium and the RL provided clinically applicable information about renal impairment for 9% and 20% of the medicines included, respectively.

Discussion

This study evaluated the availability and clinical applicability of information for rational prescribing to older patients in European and US drug compendia. The overall results indicate that the availability of relevant information is low, with 19% of information about older people available and applicable. Information about drug–drug interactions was given more often than information that more specifically concerns the older population, such as the nature of the studied population, and age-related differences in dose, efficacy, and adverse effects. If information was provided, it was usually clinically applicable, except for information about age-related differences in adverse effects and the need for monitoring in patients with renal impairment. Although statements, such as "caution is warranted in older patients" and "cautions: elderly" were often made, these are too vague to be useful for rational decision-making in daily practice. This is worrying, because older patients frequently experience adverse effects and have renal impairment. Other studies found comparable limitations in the applicability of information. For example, instructions to monitor renal or liver function were clinically applicable for only 17% of 566 instructions in European SmPCs, and instructions to monitor for haematological adverse drug reactions were adequate in 56% of 84 UK SmPCs of non-haematological drugs.[12,13]

It is remarkable that the minority of information that should be available before marketing approval, as required by the ICH E7 guideline on which the items in the current study were based, actually reaches the healthcare professionals in daily practice. This has been recognised before with respect to information provided to the FDA, which was not reflected in the PL.[14] The current study found that the overall availability and applicability of information was positively skewed by the PL in the PDR, with 68% of the information available and applicable, compared with 14% in the CM, a percentage comparable with that of the BNF and the RL. However, there were PLs for only 60% (n=21) of the medicines included in the PDR; only the CM was available for the other 13 medicines.

The combination of a concise text and a more extensive PL could be a partial solution for healthcare professionals prescribing medicines to special populations, such as older people. The Belgian Repertorium, which appeared to provide the least applicable information, incorporated a link to the SmPCs after this study was completed; however, the SmPCs do not always provide information relevant for prescribing to older people. A recent study into the availability of information about older people revealed that overall, 50% of the items described in the ICH E7 guideline were covered in SmPCs.[8] Although some items were slightly adapted for the purposes of the present study, the overall frequency is comparable with the PL.

The study has some limitations. The legislative ICH E7 guideline, which was used as a basis for data collection, focuses on what information should be available in the pre-authorisation dossier of a medicine, but not necessarily in drug compendia. However, the information given in the pre-authorisation dossier, is, or rather should be, provided in the SmPC, which in turn is the source of information for drug compendia.[1,2,5,15,16] In addition, regulatory agencies consider the SmPC and the PL the official source of basic information for use by healthcare professionals in daily practice.[17] Another point of concern is that the included compendia differed in their stated purposes. The BNF, despite its title, not only provides detailed information about individual drugs, but also aims to provide "all necessary guidance for both prescribers and dispensers,"[18] whereas the PDR is meant "for general informational purposes only".[19] This difference in intended use could influence the availability and applicability of information. A strength of the study is the large number of medicines (n=35) and compendia (n=5) investigated, so that a complete overview could be obtained of the availability and applicability of information relevant to prescribing to older patients. Moreover, it is the first study to investigate drug information of medicines commonly prescribed to older people, and the first study that analysed the online versions of the included compendia.

Drug compendia are the most commonly used sources of information for general practitioners and medical specialists.[20,21] The compendia use the SmPCs and PLs as a main source of information, [1,2,5,15,16] and for this reason, drug companies and regulatory authorities should provide enough accurate information in these documents. Because sources of information other than the SmPCs and PLs are also used, the information provided in the compendia could complement that of the SmPCs and PLs. Compendium editors should ensure that the compendium is easy to access,[22-25] reliable,[23,24] quick to use,[23,24] and that it provides applicable[26] information. Compendia are no longer printed text books, but are available online.

While compactness should no longer be an issue, readability, comprehensibility, and clinical relevance still remain important.[27] Information that is clinically applicable should optimise rational prescribing, thereby reducing the risk of safety issues.[28]

In conclusion, at the moment, the investigated compendia do not provide enough clinically applicable information about prescribing to older people, although the PDR stands head and shoulders above the other compendia as it includes the PL in an easily accessible way. Including the SmPC in the European compendia is an important step forward, but improving the amount and clinical applicability of the information about older patients in a readable way is the next step, for all compendia. Only then will healthcare professionals have a more appropriate basis for making rational decisions when prescribing to older patients.

Acknowledgements

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References

1. Belgian Centre for Pharmacotherapeutic Information (bcfi). Commented Drugs Directory and Folia Pharmacotherapeutica. Belgian Centre for Pharmacotherapeutic Information. (Accessed January, 2013, at http://www.bcfi.be/).
2. Health Care Insurance Board. Pharmacotherapeutic Compass. (Accessed January, 2013, at http://www.fk.cvz.nl/).
3. Joint Formulary Committee. British National Formulary. (Accessed January, 2013, at http://www.medicinescomplete.com).
4. Rote Liste® Service GmbH. Rote Liste®. (Accessed January, 2013, at http://www.rote-liste.de/).
5. PDR Network. Physicians› Desk Reference. (Accessed January, 2013, at http://www.pdr.net/).
6. Dutch Medicines Evaluation Board. What does a marketing authorisation dossier contain? (Accessed November 26, 2013, at http://www.cbg-meb.nl/CBG/en/human-medicines/consumers/organisation- around-medicines/What-does-a-marketing-authorisation-dossier-contain/default.htm).
7. European Medicines Agency. Studies in support of special populations: geriatrics ICH E7 (CPMP/ICH/379/95). (Accessed November 26, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002875.pdf).
8. Beers E, Egberts TCG, Leufkens HGM, Jansen PAF. Information for adequate prescribing to older patients: An evaluation of the product information of 53 recently approved medicines. *Drugs Aging* 2013; 30:255-62.
9. Steinmetz KL, Coley KC, Pollock BG. Assessment of geriatric information on the drug label for commonly prescribed drugs in older people. *J Am Geriatr Soc* 2005; 53(5):891-4.
10. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: A systematic review of the inclusion and analysis of older adults in randomised controlled trials. *J Gen Intern Med* 2011; 26(7):783-90.
11. Committee for medicinal products for human use (CHMP). Adequacy of guidance on the elderly regarding medicinal products for human use. (Accessed November 26, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500049541.pdf).
12. Geerts AFJ, De Koning FHP, Van Solinge WW, De Smet PAGM, Egberts TCG. Instructions on laboratory monitoring in 200 drug labels. *Clin Chem Lab Med* 2012; 50:1351-8.
13. Ferner RE, Coleman J, Pirmohamed M, Constable SA, Rouse A. The quality of information on monitoring for haematological adverse drug reactions. *Br J Clin Pharmacol* 2005; 60:448-51.
14. Schwartz LM, Woloshin S. Lost in transmission – FDA drug information that never reaches clinicians. *N Engl J Med* 2009; 361:1717-20.
15. Cerreta F, Eichler HG, Rasi G. Drug policy for an aging population – the European Medicines Agency's geriatric medicines strategy. *N Engl J Med* 2012; 367:1972-4.
16. British National Formulary. London: Joint Formulary Committee. (Accessed November 26, 2013, at http://www.medicinescomplete.com).
17. European Commission. A guideline on summary of product characteristics. (Accessed November 26, 2013, at http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf).
18. Kendall M, Enright D. Provision of medicines information: the example of the British National Formulary. *Br J Clin Pharmacol* 2012; 73:934-8.
19. PDR Network. Website PDR Network - Terms of Service. (Accessed November 26, 2013, at http://www.pdrnetwork.com/terms-of-service).

20. Davies K, Harrison J. The information-seeking behaviour of doctors: a review of the evidence. *Health Info Libr J* 2007; 24:78-94.

21. Hedegaard U, Damkier P. Problem-oriented drug information: physicians' expectations and impact on clinical practice. *Eur J Clin Pharmacol* 2009; 65:515-22.

22. Northup DE, Moore-West M, Skipper B, Teaf SR. Characteristics of clinical information-searching: investigation using critical incident technique. *J Med Educ* 1983; 58:873-81.

23. Timpka T, Ekstrom M, Bjurulf P. Information needs and information seeking behaviour in primary health care. *Scand J Prim Health Care* 1989; 7:105-9.

24. Dee C, Blazek R. Information needs of the rural physician: a descriptive study. *Bull Med Libr Assoc* 1993; 81:259-64.

25. Ely JW, Osheroff JA, Ebell MH, Chambliss ML, Vinson DC, Stevermer JJ, et al. Obstacles to answering doctors' questions about patient care with evidence: qualitative study. *BMJ* 2002; 324:710.

26. Connelly DP, Rich EC, Curley SP, Kelly JT. Knowledge resource preferences of family physicians. *J Fam Pract* 1990; 30:353-9.

27. Aronson JK. Drug interactions-information, education, and the British National Formulary. *Br J Clin Pharmacol* 2004; 57:371-2.

28. Cox AR, Butt TF, Ferner RE. An analysis and comparison of commonly available United Kingdom prescribing resources. *J Clin Pharm Ther* 2010; 35:453-64.

Supplementary information

TABLE S1 The drug names and therapeutic indications of the included medicinal products[1,2]

Substance name	Brand name, USA	Brand name, Europe	Therapeutic area
Ambrisentan	Letairis	Volibris	Pulmonary hypertension
Asenapine	Saphris	Sycrest	Bipolar disorder
Capsaicin	Qutenza	Qutenza	Neuralgia
Certolizumab pegol	Cimzia	Cimzia	Rheumatoid arthritis
Dabigatran	Pradaxa	Pradaxa	Replacement arthroplasty Venous thromboembolism
Degarelix	Firmagon	Firmagon	Prostate neoplasms
Denosumab	Prolia/ Xvega	Prolia	Bone resorption Postmenopausal osteoporosis
Dexamethasone	Ozurdex	Ozurdex	Macular oedema, Uveitis
Doripenem	Doribax	Doribax	Bacterial infections Ventilator-associated cross infection pneumonia
Dronedarone	Multaq	Multaq	Atrial fibrillation
Everolimus	Afinitor/ Zortress	Afinitor	Renal cell carcinoma
Febuxostat	Uloric	Adenuric	Gout
Fosaprepitant	Emend injection	Ivemend	Cancer Vomiting
Gefitinib	Iressa	Iressa	Non-small-cell lung carcinoma
Golimumab	Simponi	Simponi	Psoriatic arthritis Ankylosing spondylitis Rheumatoid arthritis
Indacaterol	Arcapta	Hirobriz/ Onbrez/Oslif	Chronic obstructive pulmonary disease
Lacosamide	Vimpat	Vimpat	Epilepsy
Lapatinib	TykerB	TyverB	Breast neoplasms
Liraglutide	Victoza	Victoza	Type 2 diabetes mellitus
Methylnaltrexone	Relistor	Relistor	Opioid-related disorders Constipation
Micafungin	Mycamine	Mycamine	Candidiasis
Ofatumumab	Arzerra	Arzerra	Chronic lymphocytic B-cell leukaemia
Paclitaxel	Abraxane	Abraxane	Breast neoplasms
Pazopanib	Votrient	Votrient	Renal cell carcinoma
Prasugrel	Effient	Efient	Unstable angina Myocardial infarction Acute coronary syndrome
Ranolazine	Ranexa	Ranexa	Angina pectoris

Substance name	Brand name, USA	Brand name, Europe	Therapeutic area
Regadenoson	Lexiscan	Rapiscan	Myocardial perfusion imaging
Rivaroxaban	Xarelto	Xarelto	Replacement arthroplasty Venous thromboembolism
Roflumilast	Daliresp	Daxas	Chronic obstructive pulmonary disease
Saxagliptin	Onglyza	Onglyza	Type 2 diabetes mellitus
Sevelamer carbonate	Renvela	Renvela	Renal dialysis Hypophosphatemia
Silodosin	Rapaflo	Silodyx/ Urorec	Prostate hyperplasia
Tocilizumab	Actemra	RoActemra	(Juvenile) rheumatoid arthritis
Tolvaptan	Samsca	Samsca	Inappropriate ADH syndrome
Ustekinumab	Stelara	Stelara	Psoriasis

TABLE S2 **Criteria for defining the clinical applicability**

Items	Information necessary for clinical applicability	Examples	Score
Age-related differences in efficacy	The efficacy in older patients	No change in efficacy in older patients	1
		Insufficient subjects ≥65y included to determine efficacy	0
Age-related differences in dose response	Specific dose recommendations for older patients	Recommend dose for older patients ≥80y is 110mg/day	1
		Dose reduction is required in patients ≥75y	0
Age-related differences in adverse events	Adverse events occurring in older patients	Bleeding (especially in older patients ≥75y)	1
		Caution in older patients	0
Influence of demographic factors on PK parameters	Influences of gender, race or ethnicity on PK parameters	C_{max} was 30% higher in females than in males	1
		Experience is limited in patients of Asian origin	0
Influence of physiological factors on PK parameters	Influences of heart, gastrointestinal, renal and liver diseases, body composition and concomitant illness on PK parameters	$T_{1/2el}$ = 12–14h in subjects with renal impairment	1
		Renal impairment would be expected to influence PK parameters	0
Extent of renal or hepatic excretion	The extent of the excretion and the form (metabolite, active substance) is mentioned	Excretion primarily unchanged in the urine	1
		Excretion both in faces and urine	0
Therapeutic range	A maximum dosage	Adults max. 800mg/day	1
		The safety of doses >10mg/day has not been evaluated	0
Absence or presence of a relevant CYP450 metabolism	Relevant CYP-enzymes or information that CYP450 metabolism plays no role in the biotransformation of the medicinal product	Converted to active metabolite via CYP3A4 and CYP2B6	1
		Metabolised in the liver	0

Items	Information necessary for clinical applicability	Examples	Score
Drug–drug interactions	Drug interactions; investigated or reasoned based on extrapolation of PK models	Avoid concomitant use of strong CYP3A4 inhibitors	1
		No drug–drug interaction studies have been conducted	0
Renally or hepatically impaired patients:			
• Why monitor*	Reasons for monitoring	Monitor renal function; impairment may increase activity	1
		Use with caution; increased risk of bleeding	0
• What to monitor*	Laboratory test is specified	Test renal function / Assess hepatic function (e.g., AST, ALT)	1
• When to start monitoring*	Moment when to start monitoring	Assess renal function before treatment	1
		Monitor for hepatic impairment	0
• When to stop monitoring*	Moment when to stop monitoring	Monitor liver function up to 4 months after initiation	1
		Assess renal function	0
• Monitoring frequency*	Frequency of monitoring	Periodically reassess renal function	1
		Monitor for worsening of renal function	0
• Critical value*	Critical value or degree of impairment	Creatinine clearance >30 mL/min / Severe hepatic impairment	1
• How to respond*	Specific therapy adjustments	Severe renal impairment: max 300mg/day	1
		Caution in patients with CrCl <50mL/min	0

Score 0 (information is not clinically applicable, 1) information is clinically applicable; ALT alanine aminotransferase; AST aspartate aminotransferase; AUC area under the curve; C_{max} maximum concentration; Cr_{Cl} creatinine clearance; CYP450 cytochrome P450 enzyme system; PK pharmacokinetic; $T_{1/2el}$ elimination half-life; * Adapted from Geerts *et al.*[3]

References

1. Website European Medicines Agency. European public assessment reports. (Accessed January 25, 2013, at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124).
2. FDA/Center for Drug Evaluation and Research. Drugs@FDA: FDA approved drug products. (Accessed December 17, 2012, at https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?CFID=2808135&CFTOKEN=feff635b9ca4e195-42E23E3A-A58D-EA93-3992C0E791FA0DF6).
3. Geerts AFJ, De Koning FHP, Van Solinge WW, De Smet PAGM, Egberts TCG. Instructions on laboratory monitoring in 200 drug labels. *Clin Chem Lab Med* 2012; 50:1351-8.

2.4

The views of healthcare professionals, drug developers and regulators on information about older people needed for rational drug prescription

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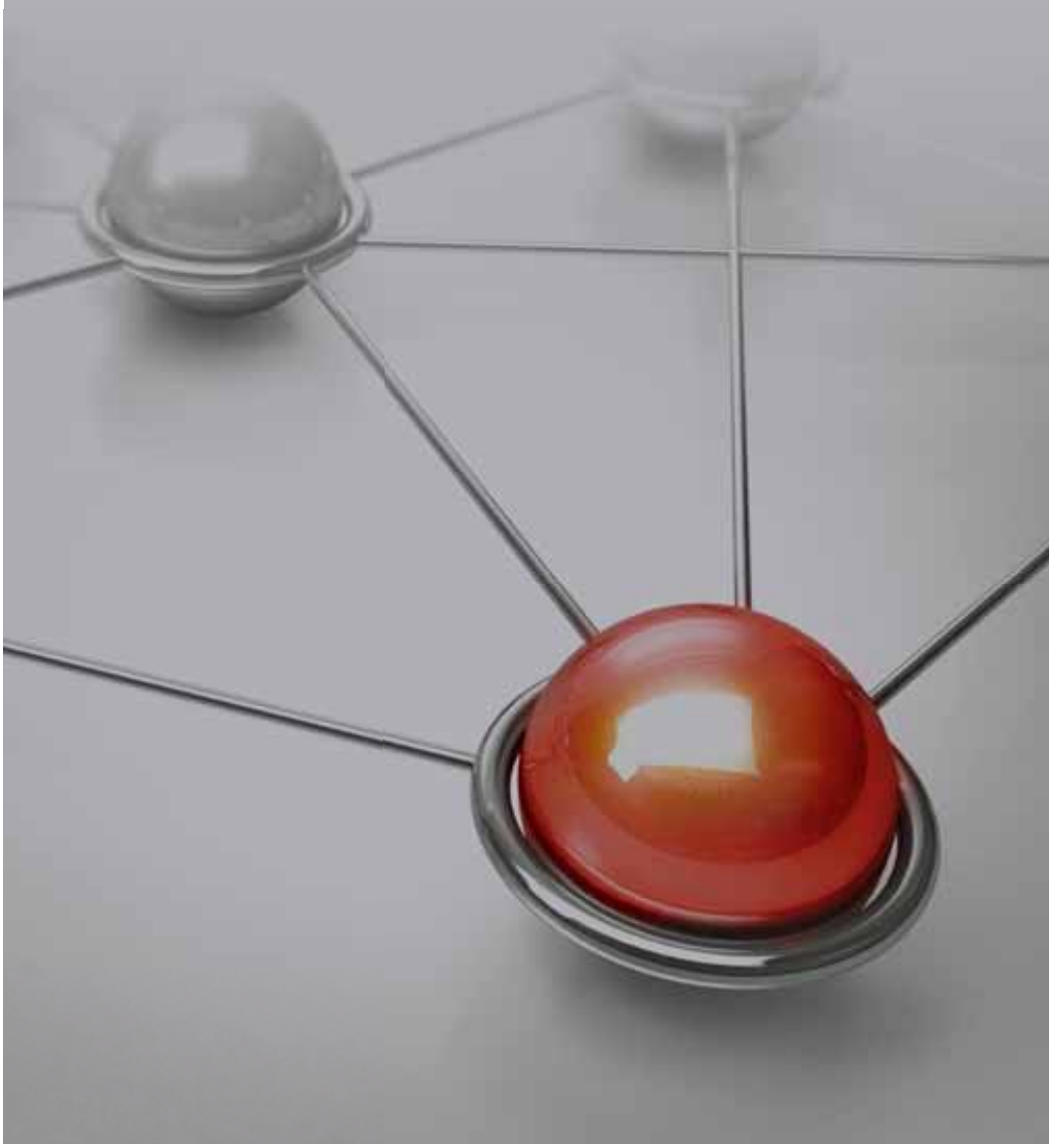


Abstract

Introduction The ICH E7 guideline intends to improve the knowledge about medicines in geriatric patients. As a legislative document, it might not reflect the needs of healthcare professionals. This study investigated what information healthcare professionals, regulatory agencies and pharmaceutical industries consider necessary for rational drug prescribing to older individuals.

Methods A 29-item-questionnaire was composed, considering the representation in trials, pharmacokinetics, efficacy, safety, and convenience of use in older individuals, with space for additions. Forty-three European professionals with an interest in medication for older individuals were included. In order to investigate their relevance, five items were included in a second questionnaire, with 11 control items. Median scores, differences between clinical and non-clinical respondents and response consistency were analysed. Consistency was present in 10 control items. Therefore, all items of the first questionnaire and the five additional items were analysed.

Results Thirty-seven (86%) respondents returned the first questionnaire; 31/37 (84%) the second. Information about age-related differences in adverse events, locomotor effects, drug–disease interactions, dosing instructions, and information about the proportion of included 65+ patients was considered necessary by most respondents. Clinicians considered information significantly more important than the nonclinical respondents about the inclusion of 75+, time to benefit in older people, anticholinergic effects, drug–disease interactions, and convenience of use. Main study limitations are the focus on information for daily practice, while the ICH E7 guideline is a legislative document focused on market approval of a new medicine. Also, a questionnaire with a Likert scale has its limitations; this was addressed by providing space for comments.

Conclusions This study reveals that items considered necessary are currently not included in the ICH E7 guideline. Also, clinicians' and non-clinicians' opinions differed significantly in 15% of the items. Therefore, all stakeholders should collaborate to improve the availability of information for the rational prescribing to older individuals.

Introduction

National guidelines, such as the British National Formulary and the Physician's Desk Reference, provide healthcare professionals with information about the rational prescribing of medicines. This information is typically based on the summary of product characteristics (SmPC) or product labelling. The SmPC is publicly available and provides information about the indication, dosing, warnings, and other basic features of medicines, and is intended as the official source of information for healthcare professionals for the effective and safe prescription of medicines.[1] The information in the SmPC as well as in the product labelling is derived from the pre-authorisation dossier.

Since in the pre-authorisation phase older people are often excluded from clinical trials[2–6], the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), a committee of the drug regulatory authorities and the pharmaceutical industry of Europe, Japan, and the United States, developed a guideline for studies involving older individuals, focusing, from a legislative point of view, on what investigations should be carried out in older people, and what information should be reported in the pre-authorisation dossier of a new medicinal product.[7] Even though the guideline is not mandatory, a sponsor or pharmaceutical industry has to provide authorities with convincing reasons why it is not following these recommendations. This ICH E7 guideline, adopted in 1994, has been updated by the questions and answers document in 2010.[8]

The ICH E7 guideline is a legislative document.[9] Consequently, it might not reflect the needs of healthcare professionals in clinical practice. Therefore, the aim of this study is to investigate the opinions of clinical and non-clinical healthcare professionals about what information regarding older individuals should be available to facilitate rational prescribing by healthcare professionals before a medicine is approved by regulatory authorities and thereby evaluating the ICH E7 guideline.

Methods

Subjects

Geriatricians, nursing home physicians, internists, pharmacists, ethicists, regulators, as well as physicians, pharmacologists and pharmacists from the pharmaceutical industry with a professional interest in medication for older individuals were selected, with the intention of creating a group of at least 30 respondents. They were selected from several working groups on the basis of their professional activities: the European Academy for Medicine of Ageing (EAMA) network, in principle two people per country; the PREDICT consortium, in principle two people per country; the Committee for Medicinal Products for Human Use (CHMP) and the European Medicines Agency (EMA), if they had experience in evaluating the pre-authorisation dossiers of medicines for older individuals; and the Geriatrics Working Party of the European Forum on Good Clinical Practice (EFGCP). Eligible members had to be accessible via e-mail; 75 professionals were invited, by email, to participate in the study.

Questionnaire

The respondents that gave written consent were asked to complete a questionnaire on the information needed to prescribe medications effectively and safely for older patients. The questionnaire contained 29 items (table S1) and was based on both the ICH E7 criteria[7] (16 items) and the questions and answers (Q&A) document[8] drawn up by the ICH (2 additional items), and the checklist of the Dutch formulary on prescribing to older patients[10] (11 additional items) (table 1). The Q&A document is supplementary to the ICH E7 guideline and intends to clarify key issues.[8] The Dutch formulary had been developed on the basis of a Delphi study involving 63 Dutch medical and pharmacological experts.

The items in the questionnaire were grouped into five themes, namely, pharmacokinetics, efficacy, and safety of medicines in older people, representation of older participants in clinical trials, and the convenience of medication use for older patients. The respondents indicated, on a Likert scale from 1 (not needed) to 10 (obligatory), whether they thought that this information should be available prior to market approval of a new medicine. A 'no opinion' option was available. Space was left for the respondents to make comments on the questionnaire or suggestions for items that should be included. Space was left for the respondents to make comments on the questionnaire or suggestions for items that should be included. The relevance of the suggestions made by the respondents was investigated by means of a second questionnaire (table S2), sent to all respondents. This second questionnaire contained the additional items suggested by the respondents as well as control items from the initial questionnaire, in order to test response consistency.

The questionnaires were sent by e-mail and respondents were allowed 2 weeks to fill in and return the questionnaire by e-mail or post of fax. Initial non-responders were sent a reminder by email after these 2 weeks.

Data analysis and statistics

Median and 10th and 90th percentiles were calculated for the responses to the questionnaire and divided in three categories, based on the median group score: 1) 'necessary information', for a median score between 7.5 and 10; 2) 'uncertain', for a median score between 3.5 and 7.5; and 3) 'unnecessary information', for a median score between 1 and 3.5.[11] Tenth and 90th percentiles are reported because they were considered to reflect the group opinion better than the range, which includes outlying single opinions.

The Mann-Whitney U test was used to examine differences between clinical respondents (physicians and pharmacists) and non-clinical respondents (regulators, pharmaceutical industry, ethicists, and scientists). The Wilcoxon signed ranks test was used to examine differences in the scores on the control items between the first and the second questionnaires. Eleven items from the initial questionnaire were used as control items in the second questionnaire. The Wilcoxon signed ranks test showed no significant differences in these items, except for the item on the convenience of use. The median score was 8.0 (10th percentile 5.8, 90th percentile 10.0) in the first questionnaire and 8.5 (10th percentile 3.0; 90th percentile 10.0) in the second (p value 0.04). Based on this response consistency, for the analyses, the results from the first questionnaire were used, together with the results on the new items from

TABLE 1 Themes and items used in the questionnaires and the sources of the items[7,8,10]

REPRESENTATION OF THE AGED	Source
Inclusion of patients ≥65 years in phase III studies	1
Inclusion of patients ≥75 years in phase III studies	1
For drugs used in diseases not unique for, but present in, old persons: inclusion of at least 100 patients ≥65 years in the phase III studies	1
For drugs used in diseases characteristically associated with aging (e.g., Alzheimer's disease): the majority of the clinical database consists of geriatric patients	1
No exclusion of patients on the basis of an upper age cut-off	1
No exclusion based on concomitant medical conditions common in old persons (e.g., cardiovascular disease, diabetes, dementia)	1
No exclusion based on concomitant treatment with drugs commonly prescribed for old persons	2
The post-marketing data collection in geriatric patients is specified in the Risk Management Plan	2
How many subjects were included in the clinical program, who were not able to sign informed consent form themselves*	4
PHARMACOKINETICS	
A single-dose pharmacokinetic study in young versus old persons	1
A multiple-dose pharmacokinetic study in young versus old persons, if there are age-related differences in pharmacokinetics	1
The extent of drug accumulation in old persons	3
The extent of renal clearance of the active substances (i.e. parent compound and/ or metabolites) in old persons	1, 3
The extent of hepatic clearance of the active substances (i.e. parent compound and/ or metabolites) in old persons	1
The therapeutic dose range of the drug	1, 3
The extent of metabolism via or effects on specified CYP450 enzymes	1, 3
Potential drug–drug interactions, if the therapeutic range of the drug or likely concomitant drugs is narrow and the likelihood of the concomitant therapy is great	1, 3
EFFICACY	
Age-related differences in efficacy	1, 3
Age-related differences in dose-response	1
If the medicinal product is indicated for a chronic condition: time to benefit in old persons	3
Information should be available about cost-effectiveness in older persons*	4
SAFETY	
Age-related differences in adverse events	1
Potential anticholinergic effects (e.g., cognitive decline, delirium, blurred vision, urine retention)	3
Potential sedative effects	3
Potential orthostatic effects	3
Potential effects on the locomotor system (e.g., decline of mobility, increased incidence of falls)	3
Potential cardiovascular side effects (e.g., arrhythmias, ischemic effects)	3
Potential effects on haemostasis (e.g., thrombotic effects, bleeding risk)	3
Potential effects on food intake (e.g., loss of appetite, stomach complaints, change of taste)	3
Important drug–disease interactions (e.g., exacerbation of heart failure)	3
Effects on the quality of life*	4
CONVENIENCE OF USE	
The convenience of use for older persons (dosage form and packaging)	3
Information should be available about dosing instructions*	4
Aspects related to medication error (invented name and pack design, suitability of a device to avoid mistakes in dosing)*	4

1) Items described in the ICH E7 guideline; 2) Items described in the questions and answers document, supplement to the ICH E7 guideline; 3) Items described in the Dutch formulary; 4) Items suggested by the respondents in first questionnaire of the present study.

the second questionnaire. Statistical analysis was performed with SPSS version 20.0 (IBM SPSS Inc., Chicago, IL, USA).

TABLE 2 Gender, specialty, and working country of the respondents

Variable	Category		Included respondents, n (%)	Initial questionnaire: respondents, n (%)	Additional questionnaire: respondents, n (%)
	Total		**43**	**37**	**31**
Gender	Male		25 (58)	21 (57)	17 (55)
	Female		18 (42)	16 (43)	14 (45)
Specialty	Clinical	**Total**	**26**	**23**	**21**
		Geriatrician	23	20	18
		Other physician*	2	2	2
		Pharmacist	1	1	1
	Non-clinical	**Total**	**17**	**14**	**10**
		Regulator	10	8	6
		Pharma group	3	3	2
		Ethicist	2	1	0
		Clinical researcher	2	2	2
Country	Austria		1	1	1
	Belgium		2	2	2
	Czech Republic		2	2	2
	Denmark		1	1	1
	Estonia		1	1	1
	Finland		1	1	1
	France		6	5	5
	Germany		4	3	0
	Greece		1	1	1
	Italy		3	3	3
	Netherlands		4	4	3
	Norway		2	1	1
	Poland		2	2	1
	Spain		2	2	2
	Sweden		1	1	1
	Switzerland		3	2	2
	United Kingdom		7	5	4

* Internist, nursing home physician

Results

Characteristics of respondents

The characteristics of the respondents are given in table 2. Of the 43 respondents included, 37 (86%) returned the initial questionnaire and 31 of these respondents (84%) returned the second questionnaire. All returned questionnaires were analysed. Not all respondents completed all items: six scores were missing and the 'no opinion' box in the initial questionnaire was checked five times. All items of the second questionnaire were completed; the 'no opinion' box was checked four times.

Fourteen of the 37 respondents (38%) made comments about or suggested additions to the first questionnaire. Some expressed having difficulty with the generalising nature of the Likert scale, and one respondent indicated that this was the reason why some items were scored 9 instead of 10. Some respondents indicated that some questions were not clearly formulated and other comments revealed that the head of the column in the first survey ("information should be available about…") was not taken into account in all items.

Six of the 31 respondents (19%) made comments about the second questionnaire, but these were more about personal opinions ("In my opinion, it is as important to have the pharmacokinetic studies in single- and multiple-dose studies, given the different body composition in older persons." or "Rather than quality of life, which is often an insensitive and difficult to interpret outcome, the influence of new therapeutic agent on Daily Life Activities and Physical Functioning is relevant.") than about poorly formulated questions.

Questionnaire Themes

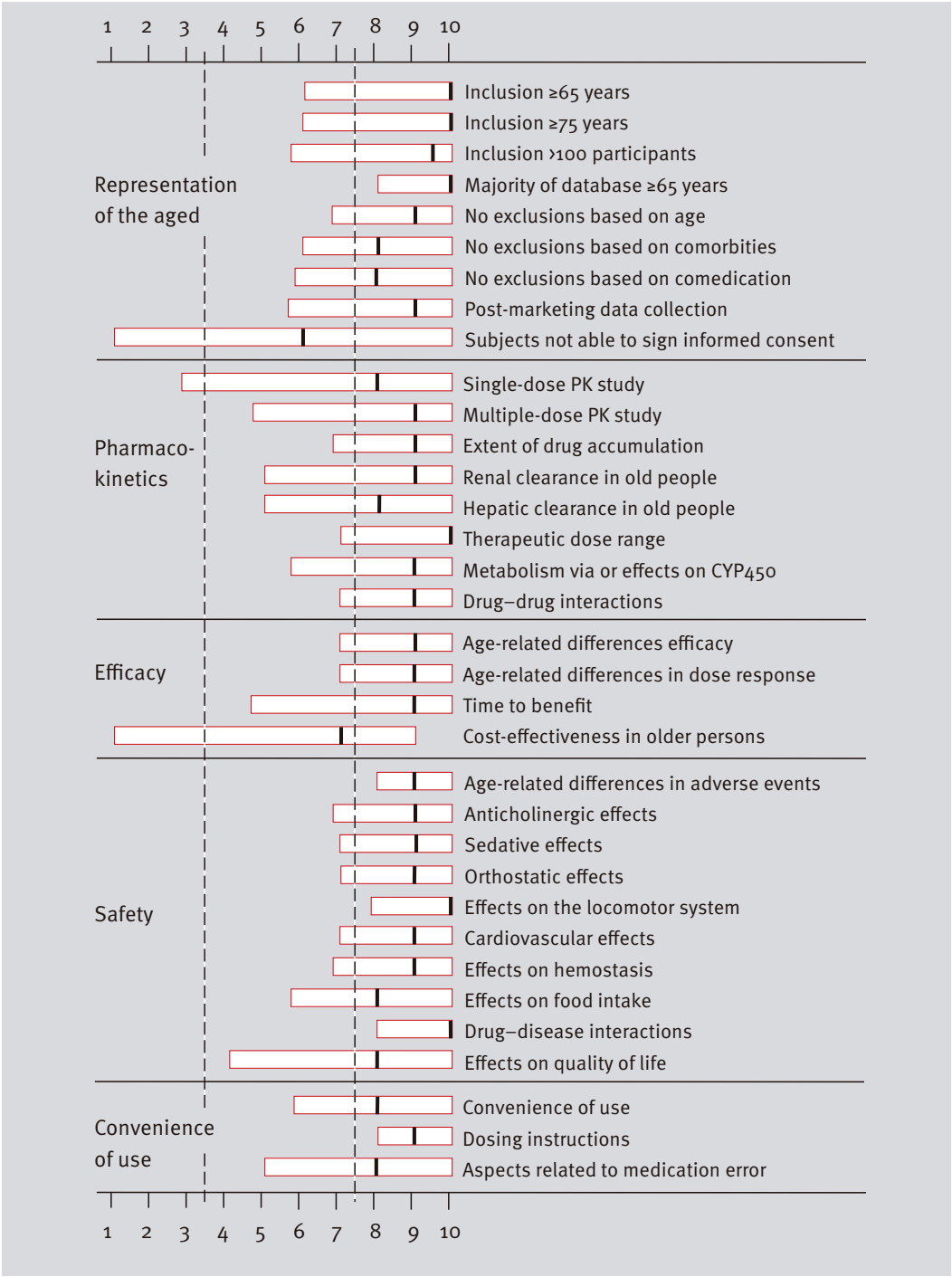
Representation of older participants in clinical trials

Figure 1 shows the overall median scores and the 10th and 90th percentiles of the respondents on the items in the first and second questionnaire.

Information about the representation of older people in clinical trials was considered necessary (median 7.5), except for the information about the number of subjects being included in the clinical program that were not able to sign informed consent themselves (median 6.0) (figure 1). All respondents considered information about the majority of the included patients being ≥65 years regarding diseases characteristically associated with aging to be essential (median score >8.0).

The respondents commented extensively on the item stating that at least 100 patients aged 65 years or older should be included in the phase III studies if a drug is indicated for a disease not unique to, but common in, old age. It was felt that, in practice, this would mean that no more than 100 patients would be included. Respondents commented that the population studied should reflect the target population. With rare diseases, it might be sufficient to recruit fewer older participants.

FIGURE 1 **Respondents' scores on the 34 items in both questionnaires**



The respondents indicated, on a Likert scale from 1 (not needed) to 10 (obligatory) (X axis), whether they thought that information on the topic (Y axis) should be available prior to market approval of a new medicine. Median and 10th and 90th percentiles are shown for the responses to the questionnaires and divided in three categories, based on the median group score: 1) 'necessary information', for a median score between 7.5 and 10; 2) 'uncertain', for a median score between 3.5 and 7.5; and 3) 'unnecessary information', for a median score between 1 and 3.5.

Pharmacokinetics in older people

All information about pharmacokinetics in older individuals was considered essential (median >7.5) (figure 1). More respondents considered information about multiple-dose pharmacokinetic studies in older patients to be more important (median 9.0; 10th percentile 5.5) than information on single-dose pharmacokinetic studies in older patients (median 8.0; 10th percentile 3.6; $p<0.05$). Information about the renal clearance of a drug was considered more important (median 9.0; 10th percentile 5.6) than information about the hepatic clearance of the drug (median 8.0; 10th percentile 5.0; $p<0.05$). Most respondents considered information about the therapeutic dose range to be obligatory (median 10.0; 10th percentile 7.0).

Efficacy of medicines in older people

The respondents considered information about age-related differences in efficacy and dose-response to be essential (median 9.0; 10th percentile 7.0) (figure 1). Information about the time to benefit in older people was also considered necessary, but the range of responses was wider (median 9.0; 10th percentile 5.0). Respondents were less certain about the importance of information on cost-effectiveness in older people (median 7.0; 10th percentile 1.0).

Safety of medicines in older people

All respondents considered information about age-related differences in adverse events (median 9.0; 10th percentile 8.0), effects on the locomotor system (median 10.0; 10th percentile 8.0), and drug–disease interactions (median 10.0; 10th percentile 8.0) to be necessary (figure 1), and most respondents considered information about how a drug affects food intake (median 8.0; 10th percentile 6.0) and quality of life (median 8.0; 10th percentile 4.0) to be important, but scores showed more variation.

Convenience of use for older patients

Most respondents considered information about the convenience of medication use in older people (i.e. about dosing forms and packaging) (median 8.0; 10th percentile 5.0) and information about aspects related to medication errors, such as the pack name and design and the suitability of a device to avoid mistakes in dosing (median 8.0; 10th percentile 4.0), to be important (figure 1). All respondents agreed that information on dosing instructions was essential (median 9.0; 10th percentile 8.0).

Clinical vs. non-clinical professionals

On most items, the opinions of the non-clinical respondents, i.e. regulators, professionals from the pharmaceutical industry, an ethicist, and a researcher, were not significantly different from those of the clinical respondents (physicians and pharmacists) (table 3). However, while both clinical and non-clinical respondents considered information about the inclusion of patients aged 65 years or older important, the non- clinical respondents considered information about the inclusion of patients aged 75 years and older less important than did the clinical respondents (median 8.0, interpercentile range 5.5–10.0 versus median 10.0, interpercentile range 8.3–10.0, respectively; $p<0.05$). The same was true for information about the time to benefit for drugs for chronic use (clinical respondents median 9.0, interpercentile range 6.0–10.0 versus non-clinical respondents median 7.0, interpercentile range 1.4–9.6;

TABLE 3 Differences in scores between clinical and non-clinical respondents

Item	Clinical respondents median (10^{th}, 90^{th} percentile)	Non-clinical respondents median (10^{th}, 90^{th} percentile)	p value
REPRESENTATION OF THE AGED			
Inclusion ≥65 years	10.0 (6.4-10.0)	8.5 (6.0-10.0)	0.16
Inclusion ≥75 years	**10.0 (8.3-10.0)**	**8.0 (5.5-10.0)**	**<0.05**
Inclusion ≥100 patients ≥65 years	9.0 (6.0-10.0)	9.0 (2.6-10.0)	0.77
Majority of database ≥65 years	10.0 (8.0-10.0)	9.5 (7.0-10.0)	0.63
No exclusions based on age	9.0 (8.0-10.0)	8.5 (6.0-10.0)	0.14
No exclusions based on comorbidities	8.0 (6.8-10.0)	7.5 (5.0-10.0)	0.09
No exclusions based on comedication	8.0 (6.4-10.0)	8.5 (5.0-10.0)	0.48
Post-marketing data collection	9.0 (5.2-10.0)	10.0 (4.0-10.0)	0.08
Subjects not able to sign informed consent form*	8.0 (1.0-10.0)	5.0 (1.1-8.9)	0.17
PHARMACOKINETICS			
Single-dose PK study	9.0 (3.2-10.0)	7.5 (2.0-10.0)	0.29
Multiple-dose PK study	9.5 (5.3-10.0)	8.0 (2.5-10.0)	0.09
Extent of drug accumulation	9.0 (7.0-10.0)	8.0 (6.0-10.0)	0.17
Renal clearance in old people	10.0 (6.0-10.0)	8.0 (1.5-10.0)	0.08
Hepatic clearance in old people	8.0 (6.0-10.0)	8.0 (1.5-10.0)	0.34
Therapeutic dose range	10.0 (7.3-10.0)	9.5 (5.5-10.0)	0.33
Metabolism via or effects on CYP450	9.0 (5.4-10.0)	9.0 (5.4-10.0)	0.52
Drug–drug interactions	10.0 (7.4-10.0)	9.0 (4.5-10.0)	0.10
EFFICACY			
Age-related differences in efficacy	9.0 (8.0-10.0)	8.5 (6.0-10.0)	0.18
Age-related differences in dose-response	9.0 (8.0-10.0)	9.0 (6.0-10.0)	0.25
Time to benefit	**9.0 (6.0-10.0)**	**7.0 (1.4-9.6)**	**<0.05**
Cost-effectiveness in older persons*	8.0 (5.0-9.0)	2.0 (1.0-9.2)	0.11
SAFETY			
Age-related differences in adverse events	9.0 (8.0-10.0)	9.5 (8.0-10.0)	0.82
Anticholinergic effects	**10.0 (7.4-10.0)**	**8.0 (4.5-10.0)**	**<0.05**
Sedative effects	10.0 (8.0-10.0)	8.5 (6.0-10.0)	0.09
Orthostatic effects	10.0 (7.4-10.0)	8.0 (6.0-10.0)	0.07
Effects on the locomotor system	10.0 (8.4-10.0)	9.0 (4.5-10.0)	0.15
Cardiovascular effects	9.0 (8.0-10.0)	9.5 (7.0-10.0)	0.77
Effects on haemostasis	9.0 (7.4-10.0)	9.5 (5.0-10.0)	0.79
Effects on food intake	9.0 (6.0-10.0)	7.5 (5.0-10.0)	0.06
Drug–disease interactions	**10.0 (8.4-10.0)**	**9.0 (7.5-10.0)**	**<0.05**
Effects on quality of life*	8.0 (6.0-10.0)	6.0 (2.1-9.9)	0.08
CONVENIENCE OF USE			
Convenience of use	**9.0 (6.4-10.0)**	**7.0 (5.0-10.0)**	**<0.05**
Dosing instructions*	9.0 (8.0-10.0)	9.5 (7.1-10.0)	0.87
Aspects related to medication error*	8.0 (5.0-9.9)	7.0 (5.1-10.0)	0.98

* Items of the second questionnaire

p<0.05). The non-clinical respondents considered information about anticholinergic effects to be less important than did the clinical professionals (median 8.0, interpercentile range 4.5–10.0 and median 10.0, interpercentile range. 7.4–10.0, respectively; p<0.05). This was also the case for information about drug–disease interactions, such as exacerbation of heart failure caused by a medicine prescribed for a different indication (nonclinical respondents median 9.0, interpercentile range 7.5–10.0 versus clinical respondents median 10.0, interpercentile range 8.4–10.0, respectively; p<0.05).

Information about the convenience of use was considered more important by the clinical respondents (median 9.0, interpercentile range 6.4–10.0) than by the non-clinical respondents (median 7.0, interpercentile range 5.0–10.0; p<0.05).

Information about five of the ten items rated by the clinical respondents as being most important (10th percentile >8.0), namely, information about the sedative, cardiovascular, locomotor effects, drug–disease interactions, and dosing instructions for older patients, is not described in the ICH E7 guideline or in the Q&A document.

Discussion

This study investigated which information about older patients clinical and non-clinical professionals consider should be included in the registration dossier for a new medicine. All respondents thought providing information about older people is important and considered information about the inclusion of older participants in the clinical development program obligatory. This reflects the current discussion about older people still being underrepresented in studies of many diseases associated with aging, such as acute coronary syndrome[4], heart failure[12] and Parkinson's disease[13] even though the Food and Drug Administration, the European Medicines Agency, and clinicians have stressed the importance of including more older participants in clinical trials.[3,5,7,8,14,15]

Information about the therapeutic dose range was considered very important, as was the information about age-related differences in adverse events, drug–disease interactions, and dosing instructions. The first two items are included in the ICH E7 guideline. A previous study showed that information about age-related differences in adverse events was included in 40% (21/53) of the SmPCs and in 74% (39/53) of the European public assessment reports (EPARs), the public surrogate of the pre-authorisation dossier.[16] Information about the therapeutic dose range could be found in 51% (27/53) of the SmPCs and in 89% (47/53) of the EPARs. Thus, the information considered very important by healthcare professionals appears to be covered in pre-authorisation dossiers.

The stipulation that at least 100 participants aged ≥65 years should be included in trials comes from the ICH E7 guideline, which also states that the composition of the study population should reflect that of the general population.[7] In the Q&A document, the EMA emphasised that more than 100 patients is usually appropriate in phase II and III studies.[8] A study on the number of older patients included in the phase II and phase III trials of recently

registered drugs showed that about 15% of participants included in trials for two medicines for diabetes mellitus type II (both marketed since 2009) were aged 65 years and older, with a minimum of 108 and a maximum of 887 older participants (Beers E *et al.*, unpublished data); about 1% of the study population was aged 75 years and older (n= 55–83). This small proportion of older adults is striking given that most people with diabetes in developed countries are 65 years or older.[17]

Inter-professional differences

A striking finding was that the non-clinical respondents considered information about the inclusion of participants older than 75 years significantly less important than did the clinical respondents. Even so, the non-clinical respondents considered it more important to mention information about the inclusion of patients older than 65 years than information about the inclusion of patients aged 75 years and older, while the reverse was true for the clinical respondents. As is a commonly accepted theory, the risk of frailty increases with age, and frailty is accompanied by a higher risk of adverse outcomes.[18] Therefore, it is perhaps to be expected that the clinical respondents considered information about this age range important. The non-clinical respondents were also less concerned than the clinical respondents about the inclusion of information about the drug's potential to cause anticholinergic effects. This is surprising because drugs with anticholinergic potential are regarded inappropriate in the older population; both the American Beers list[19] and the European START-STOPP criteria[20] recommend that this group of medicines should be avoided. As the anticholinergic load correlates with the severity of adverse events[21], it is important to have this information available in daily clinical practice.

The non-clinical respondents also considered the convenience of drug use, such as dosage form and packaging, to be less important, although several studies have shown that difficulties with drug dosing and packaging are common, especially among older patients, and give rise to problems ranging from mild inconvenience to serious complications.[22]

Information about the time to benefit in old persons for medicines intended for chronic use was considered significantly more important by the clinical. It is perhaps to be expected that the non-clinical professionals attached less importance to the concept of time to benefit, since they are aware that clinical trial duration mostly is relatively short, resulting in the concept of time to benefit being difficult to use, especially for a subgroup of, sometimes underrepresented, older patients.[23]

These results are consistent with the professional differences recently found by Crome *et al.*, in which geriatricians, general practitioners, nurses, ethicists, clinical researchers as well as pharmacologists and pharmacists working in the pharmaceutical industry from nine European countries were asked for their opinions on the exclusion of older people.[14] Geriatricians as a group were most likely to agree with the statement that older people are under-represented in clinical trials, that older people were disadvantaged by this under-representation and that, as a result, healthcare professionals experience difficulties in prescribing medication to older patients.

Study strengths and limitations

The focus of this study was on the information about older patients for the rational prescription of medicines from a healthcare professional's point of view. Although the ICH E7 guideline and its supplementary Q&A document have the same goal, their focus is on legislative aspects.[7,8] The current study suggests that the ICH E7 guideline is not yet optimal.

A strength of this study is that the respondents were given the opportunity to comment on the questionnaire, which resulted in the inclusion of five new items in the second questionnaire. The response consistency between the two questionnaires was considered adequate. Further, it was explicitly stated that information should be needed to know, rather than nice to know, in order to filter out individual wishes.[24] The respondents came from several European countries, thereby covering inter-country differences, as was also seen in a recent study investigating the professional views on the exclusion of older people from clinical trials in nine European countries.[14]

A potential source of bias is that the respondents willing to participate in this study might have been particularly concerned about the availability of information on older patients. Moreover, not all the professional groups were represented in satisfying number and this was especially the case for the pharmaceutical industry and for the sole pharmacist. This problem was partly addressed by creating groups of clinical and non-clinical professionals. Another limitation is that no general practitioners were selected, although in several countries, they are responsible for the prescription of medication to older patients. Furthermore, although we originally intended to include five representatives from individual countries, the response rate differed greatly between the countries, a difficulty recognised earlier by Crome *et al.*[14]

The limitations of a questionnaire are clear: it can be difficult to award answers a score from 1 to 10 and answers may depend on the therapeutic indication or on the behaviour of a drug in the body. This might have influenced the answers given to the pharmacokinetic items and the items on the representation of the older individuals in particular, with the respondents giving lower scores as a reflection of this uncertainty. It was apparent that not all respondents took the column heading ("information should be available about…") into account, but this issue was resolved in the second questionnaire. However, since the control items were consistently answered in the two questionnaires, the phrasing may have not played a major role.

Next steps

As mentioned above, the results suggest that the ICH and/or the EMA could improve the information base about the rational use of medicines in the older population, especially with regard to safety aspects. The ICH E7 guideline does state that there should be an evaluation of age-related differences in adverse events, but it has become clear that clinical professionals need more specific information about the safety aspects of medicines, such as sedative, cardiovascular, and locomotor effects, as well as information about drug–disease interactions and dosing instructions for older patients. Crome *et al.* found that respondents from pharmaceutical industries were least likely to respond that clinical trial regulation needs to be amended, although 56% still did so. The present arrangements for the inclusion of older participants,

such as the ICH E7, were considered unsatisfactory by the majority of the geriatricians and nurses.[14]

One of the limitations of the present study was the low number of representatives of the groups of pharmacists and pharmaceutical industries and the lack of inclusion of general practitioners. These issues should be addressed in future research as well as in policy making. Fortunately, several steps have already been taken, such as the institution of the Geriatric Expert Group by the EMA, which involves different clinical practitioners, as well as the PREDICT Charter that aims to promote the inclusion of older people in clinical trials, to prevent discrimination on the base of age and to defend the rights of older people in clinical trials.[25]

Conclusions

All respondents thought providing information about older people is important. A number of items considered most important are currently not included in the ICH E7 guideline or its supplement, the Q&A document, namely, information about effects on the locomotor system, drug–disease interactions, and dosing instructions. This suggests that the ICH E7 guideline should be optimised, moreover since the views of the regulatory authorities and the pharmaceutical industry differ from those of the clinical practitioners on the relevance of information in the pre-authorisation dossier of new medicines. Since the latter are the people who have to advice on or to prescribe medication to frail, older patients, more practical information should be available. The pre-authorisation dossier would seem to be the appropriate document for this information, because it is used to prepare the EPAR as well as in the SmPC and PI. It is important that all stakeholders participate in efforts to improve the availability of information about older people to clinical practitioners.

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References

1. European Commission. A guideline on summary of product characteristics. (Accessed December 9, 2013, at http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf).
2. Bartlett C, Davey P, Dieppe P, Doyal L, Ebrahim S, Egger M. Women, older persons, and ethnic minorities: factors associated with their inclusion in randomised trials of statins 1990 to 2001. *Heart* 2003; 89(3):327-8.
3. Cherubini A, Del Signore S, Ouslander J, Semla T, Michel JP. Fighting against age discrimination in clinical trials. *J Am Geriatr Soc* 2010; 58(9):1791-6.
4. Dodd KS, Saczynski JS, Zhao Y, Goldberg RJ, Gurwitz JH. Exclusion of older adults and women from recent trials of acute coronary syndromes. *J Am Geriatr Soc* 2011; 59(3):506-11.
5. McMurdo ME, Roberts H, Parker S, Wyatt N, May H, Goodman C, et al. Improving recruitment of older people to research through good practice. *Age Ageing* 2011; 40(6):659-65.
6. McMurdo ME, Witham MD, Gillespie ND. Including older people in clinical research. *BMJ* 2005; 331(7524):1036-7.
7. European Medicines Agency. Studies in support of special populations: geriatrics ICH E7 (CPMP/ICH/379/95). (Accessed April 16, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002875.pdf).
8. Committee for medicinal products for human use (CHMP). ICH topic E7 studies in support of special populations: geriatrics; questions and answers. (Accessed April 16, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500005218.pdf).
9. Molzon JA, Giaquinto A, Lindstrom L, Tominaga T, Ward M, Doerr P, et al. The value and benefits of the international conference on harmonisation to drug regulatory authorities: Advancing harmonization for better public health. *Clin Pharmacol Ther* 2001; 89: 503-12.
10. Huisman-Baron M, van der Veen L, Jansen PA, van Roon EN, Brouwers JR, van Marum RJ. Criteria for drug selection in frail elderly persons. *Drugs Aging* 2001; 28: 391-402.
11. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Làzaro P, et al. The RAND/UCLA appropriateness method user's manual. Santa Monica: RAND. 2001, Santa Monica.
12. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011; 171(6):550-6.
13. Fitzsimmons PR, Blayney S, Mina-Corkill S, Scott GO. Older participants are frequently excluded from Parkinson's disease research. *Parkinsonism Relat Disord* 2012;18(5):585-9.
14. Crome P, Lally F, Cherubini A, Oristrell J, Beswick AD, Clarfield AM, et al. Exclusion of older people from clinical trials: Professional views from nine European countries participating in the PREDICT study. *Drugs Aging* 2011; 28: 667-77.
15. Witham MD, McMurdo ME. How to get older people included in clinical studies. *Drugs Aging* 2007; 24(3):187-96.
16. Beers E, Egberts TCG, Leufkens HGM, Jansen PAF. Information for adequate prescribing to older patients: An evaluation of the product information of 53 recently approved medicines. *Drugs Aging* 2013; 30: 255-62.
17. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27: 1047-53.
18. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: Evidence from the Canadian national population health survey. *CMAJ* 2001; 183: E487-94.

19. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American geriatrics society updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2012; 60: 616-31.

20. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (screening tool of older person's prescriptions) and START (screening tool to alert doctors to right treatment). Consensus validation. *Int J Clin Pharmacol Ther* 2008; 46: 72-83.

21. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med* 2008; 168: 508-13.

22. Ward J, Buckle P, John Clarkson P. Designing packaging to support the safe use of medicines at home. *Appl Ergon* 2010; 41: 682-94.

23. Holmes HM, Hayley DC, Alexander GC, Sachs GA. (2006) Reconsidering medication appropriateness for patients late in life. *Arch Intern Med* 2006; 166: 605- 9.

24. Rahmner PB, Eiermann B, Korkmaz S, Gustafsson LL, Gruven M, Maxwell S, et al. Physicians' reported needs of drug information at point of care in Sweden. *Br J Clin Pharmacol* 2012; 73: 115-25.

25. PREDICT Consortium. PREDICT charter for the rights of older people in clinical trials. (Accessed April 16, 2013, at http://www.predicteu.org/PREDICT_Charter/predict_charter.html).

Supplementary information

TABLE S1 First questionnaire containing 29 items

	ITEMS	not needed								obligatory		no opinion
	Information should be available about:	1	2	3	4	5	6	7	8	9	10	
1	Inclusion of patients ≥65 years in phase III studies	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2	Inclusion of patients ≥75 years in phase III studies	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3	For drugs used in diseases not unique for, but present in, old persons: inclusion of at least 100 patients ≥65 years in the phase III studies	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4	For drugs used in diseases characteristically associated with aging (e.g. Alzheimer's disease): the majority of the clinical database consists of geriatric patients	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5	No exclusion of patients on the basis of an upper age cut-off	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6	No exclusion based on concomitant medical conditions common in old persons (e.g. cardiovascular disease, diabetes, dementia)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7	No exclusion based on concomitant treatment with drugs commonly prescribed for old persons	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8	Age-related differences in efficacy	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9	Age-related differences in dose-response	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10	Age-related differences in adverse events	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
11	A single-dose pharmacokinetic study in young versus old persons	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
12	A multiple-dose pharmacokinetic study in young versus old persons, if there are age-related differences in pharmacokinetics	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
13	The extent of drug accumulation in old persons	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
14	The extent of renal clearance of the active substances (i.e. parent compound and/ or metabolites) in old persons	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
15	The extent of hepatic clearance of the active substances (i.e. parent compound and/ or metabolites) in old persons	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	ITEMS	not needed									obligatory	no opinion
16	Potential anticholinergic effects (e.g. cognitive decline, delirium, blurred vision, urine retention)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
17	Potential sedative effects	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
18	Potential orthostatic effects	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
19	Potential effects on the locomotor system (e.g. decline of mobility, increased incidence of falls)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
20	Potential cardiovascular side effects (e.g. arrhythmias, ischemic effects)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
21	Potential effects on haemostasis (e.g. thrombotic effects, bleeding risk)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
22	Potential effects on food intake (e.g. loss of appetite, stomach complaints, change of taste)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
23	The therapeutic dose range of the drug	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
24	The extent of metabolism via or effects on specified CYP450 enzymes	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
25	Potential drug–drug interactions, if the therapeutic range of the drug or likely concomitant drugs is narrow, and the likelihood of the concomitant therapy is great	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
26	Important drug–disease interactions (e.g. exacerbation of heart failure)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
27	If the medicinal product is indicated for a chronic condition: time to benefit in old persons	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
28	The convenience of use for older persons (dosage form and packaging)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
29	The post-marketing data collection in geriatric patients is specified in the Risk Management Plan	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

TABLE S2 **Additional questionnaire containing five items suggested by the respondents and 11 control items**

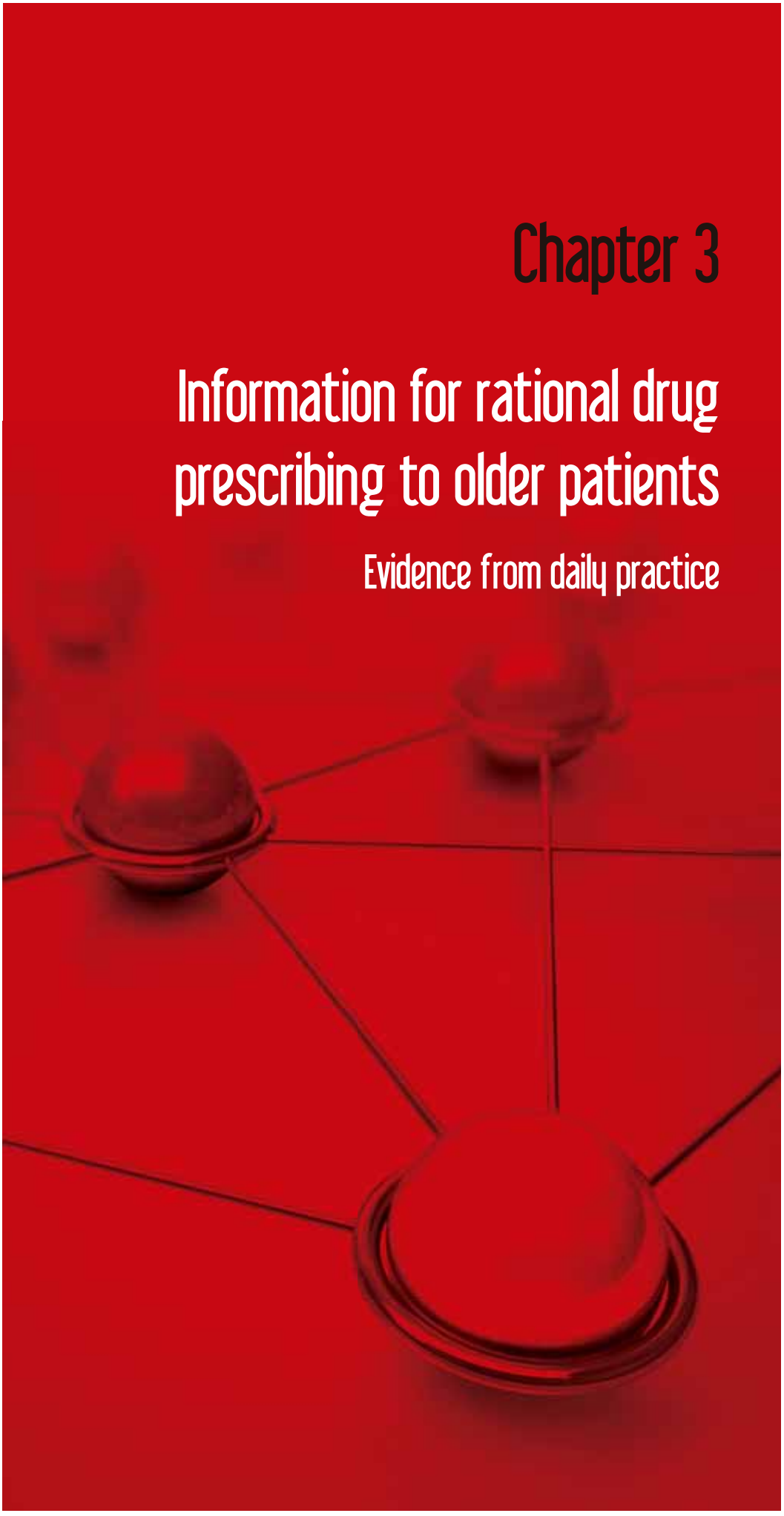
	ITEMS	not needed								obligatory		no opinion
		1	2	3	4	5	6	7	8	9	10	
a	For drugs used in diseases not unique for, but present in, old persons: information should be available about whether at least 100 patients ≥65 years in the phase III studies have been included	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
b	Information should be available about a single-dose pharmacokinetic study in young versus old persons	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
c	Information should be available about the convenience of use for older persons (dosage form and packaging)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
d	Information should be available about a multiple-dose pharmacokinetic study in young versus old persons, if there are age-related differences in pharmacokinetics	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
e	Information should be available about effects on the quality of life	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
f	Information should be available about the extent of renal clearance of the active substances (i.e. parent compound and/ or metabolites) in old persons	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
g	Information should be available about the extent of hepatic clearance of the active substances (i.e. parent compound and/ or metabolites) in old persons	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
h	Information should be available about cost-effectiveness in older persons	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
i	Information should be available about dosing instructions	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
j	Information should be available about the extent of metabolism via or effects on specified CYP450 enzymes	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
k	Information should be available about the extent of drug accumulation in old persons	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
l	Information should be available about potential sedative effects	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
m	Information should be available about potential cardiovascular side effects (e.g. arrhythmias, ischemic effects)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	ITEMS	not needed									obligatory	no opinion
n	Information should be available about how many subjects were included in the clinical program, who were not able to sign informed consent form themselves	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
o	Important drug–disease interactions (e.g. exacerbation of heart failure)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
p	Information should be available about aspects related to medication error (invented name and pack design, suitability of a device to avoid mistakes in dosing)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Chapter 3

Information for rational drug prescribing to older patients

Evidence from daily practice



3.1

Upper gastrointestinal events associated with non-selective NSAIDs and coxibs in older people in daily practice

A retrospective cohort study and comparison with randomised clinical trials

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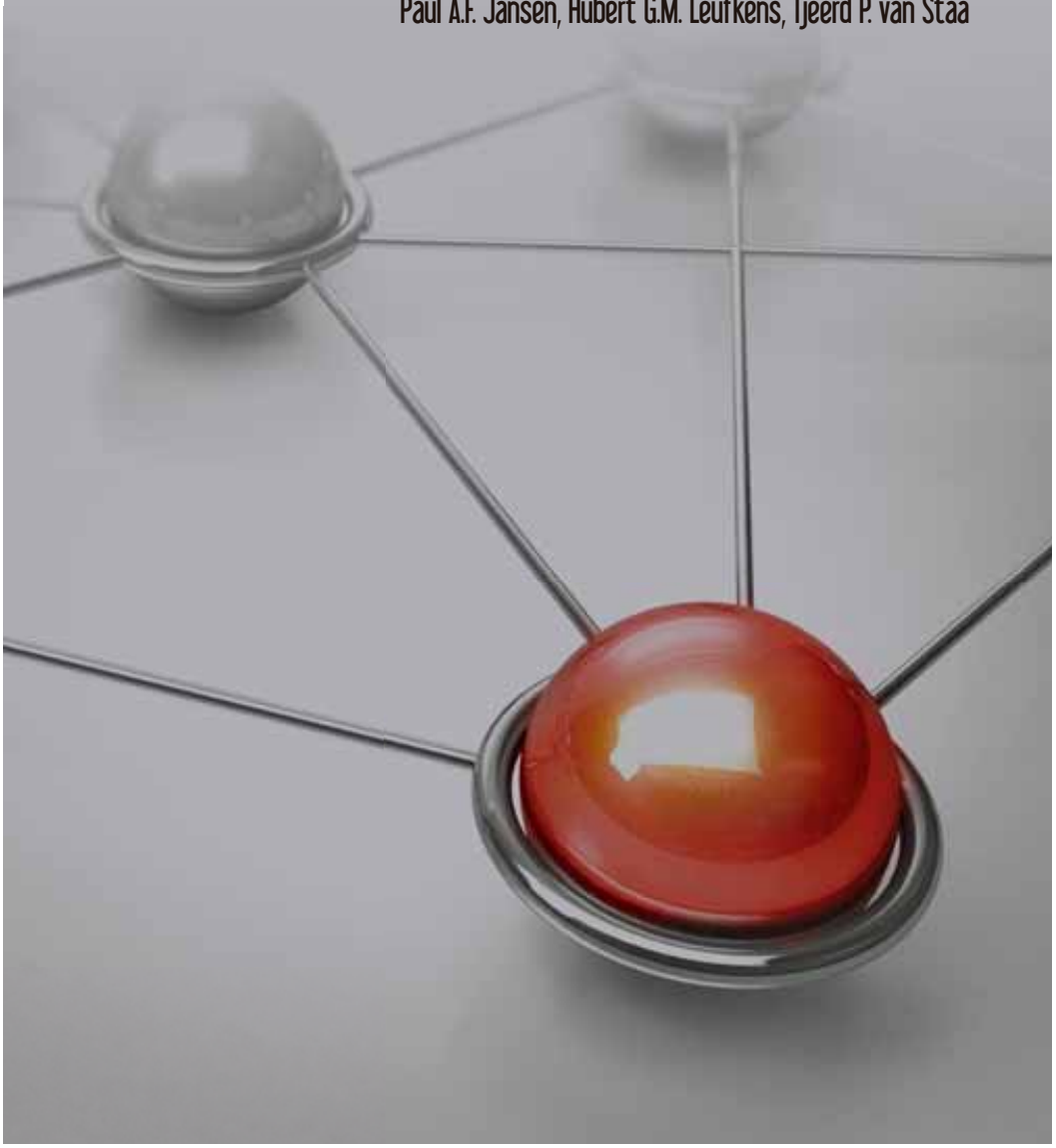

Abstract

Introduction The aims of this study were to evaluate the absolute risk of upper gastrointestinal (GI) events during non-selective NSAID (nsNSAID) use and use of cyclooxygenase-2-inhibitors (coxibs) in patients aged 65–74 years and ≥75 years in daily practice, and to compare the magnitude of these risks with those reported in randomised clinical trials (RCTs).

Methods A retrospective cohort study and a descriptive comparison with RCTs was performed with use of records from the UK Clinical Practice Research Datalink (CPRD; from January 1995 to March 2013). Large RCTs (≥2,000 patients) or meta-analyses of RCTs comparing coxibs with nsNSAIDs with incidence rates (IRs) of upper GI events as primary outcome measure were included. Participants were patients aged ≥65 years with a prescription for an nsNSAID or a coxib, irrespective of exposure time, indication or frequency of use, were followed from their first nsNSAID or coxib prescription for the occurrence of an upper GI event. Main outcome measures were IRs (events/1,000 person-years) of upper GI events in nsNSAID and coxibs users aged 65–74 years and ≥75 years.

Results The IRs of upper GI events in the 714,224 patients included in the study were highest in first-time users, and in patients using nsNSAIDs or coxibs on a daily basis for less than 6 months. The upper GI risks did not differ substantially between nsNSAID and coxibs users. A consistent age effect was seen in both medication groups. In the RCTs, the IRs in nsNSAID users were 2.5–13.5 times higher compared with daily practice, and in subjects aged ≥75 years 19 times higher. For coxib users, the IRs found in RCTs were less than 5 times higher, also for those aged ≥75 years.

Conclusions The frequencies of upper GI events in older patients using nsNSAIDs and coxibs in general practice were lower than has been suggested by findings of RCTs. However, reported rates in RCTs varied highly and our research findings may be affected by differences in baseline risks of the studied populations and in the way GI events were quantified. Observational studies in daily practice remain important to add insight to what has been learned from RCTs.

Introduction

A major aim of clinical drug trials is to investigate a medicine in a relatively homogenous study population for methodological, ethical and practical reasons. Exclusion criteria concerning age, comorbidities and polypharmacy have been limiting consistently the participation of older people in such trials, particularly those aged 75 years or older; thereby affecting the generalizability of the efficacy and safety findings.[1-7] This has been especially flagged as a critical issue for the safety evaluation in older people with multiple risk factors, as they are at a greater risk of adverse drug reactions (ADRs) and medication-related hospitalisations.[8-10]

Non-steroidal anti-inflammatory drugs (NSAIDs) as a drug class have been frequently associated with drug induced gastrointestinal (GI) bleedings. NSAIDs appeared to account for 14.5% of unplanned hospital admissions in the Netherlands, whereas they were most commonly involved in 29.6% of all ADR-related hospital admissions in the UK.[8,10] In the latter study, GI bleeding was the most commonly seen ADR associated with non-selective NSAIDs (nsNSAIDs) other than aspirin. In comparison with nsNSAIDs, cyclooxygenase-2-inhibitors (coxibs) are well known for their relatively lower risk of upper GI events.[11-20]

The lower GI risk for coxibs compared with nsNSAIDs has been also confirmed in RCTs for patients aged ≥65 years.[17,19,20] However, it remains unclear whether these findings also apply to older, i.e. 65–74 years and ≥75 years, people in daily practice having multiple risk factors including comorbid conditions, exposed to polypharmacy, impaired renal function, and the like.[7]

The aim of this study is to quantify absolute upper GI risk in patients aged 65–74 years and ≥75 years during use of nsNSAID or coxibs in daily practice and to compare the magnitude of these risks with those reported in RCTs.

Methods

Data for this study were obtained from the Clinical Practice Research Datalink (CPRD). The design and the definitions in this study were similar to the published study by van Staa *et al.* concerning the cost-effectiveness of nsNSAIDs and coxibs comparing data on GI safety from CPRD with published RCT data on the topic [21]. CPRD contains computerised medical records from 650 affiliated general practices covering over 10 million patients in the UK. In the UK, general practitioners play a key role in the healthcare system; they are responsible for primary healthcare and referrals to other sectors in the system. Data recorded in the CPRD include demographic information, diagnosis, prescription details, clinical events, specialist referrals and hospital admissions and major clinical outcomes.

Study design

A retrospective cohort study was conducted in two groups of patients aged 65–74 years and ≥75 years with a first prescription for a nsNSAID or a coxib between January 1995 and March 2013. Patients were eligible to be included in the study if they had at least one year of valid data collection prior to the index date. The date of the first prescription marked the start of follow-up. Patients were followed from cohort entry until the study end date (March 2013) or until the patient died or was transferred out of the practice, whichever came first. In these two groups we quantified unadjusted absolute upper GI risk, i.e. number of events per 1,000 person-years. The reason not to adjust was driven by the intend to mimic and compare with those reported in RCTs, the occurrences of upper GI risk in different exposure groups as directly observed in general practice.

Exposure

The NSAIDs included were those available on the UK market at the time of the study. In order to determine the exposure characteristics (daily or intermittent use, and short–term or long–term use), the longitudinal prescription histories of the CPRD were analysed. The medication possession ratio (MPR), i.e., the proportion of time covered by medication use, was estimated for each individual NSAID prescription with a prior prescription in CPRD in the 6 months before. Current as well as past exposure to nsNSAIDs or coxibs were evaluated using the following definitions: *current exposure* was the time period from the prescription date up to three months after the end of the prescription or to the date that a new prescription was recorded within this period; *recent exposure* was the period 3 to 6 months after the end of the prescription; and exposure was classified as *past exposure* when there was a gap of >6 months after the end of the last prescription. Because of the time-dependent classification, patients could move between different exposure groups over time. At the start of each interval, each patient was classified as a *current* user of NSAID medication if he or she had an NSAID prescription on the start date or within the three months before. Current NSAID users were classified as:

1. Starters: patients on the first NSAID prescription issued at least one year after January 1995;
2. Continuous users: patients who had been prescribed NSAIDs repeatedly in the preceding 6 months:
   - **a** Quarterly use; i.e., low MPR (<0.40);
   - **b** Monthly use; i.e., medium MPR (0.40–0.59);
   - **c** Weekly use; i.e., high MPR (0.60–0.79);
   - **d** Daily use; i.e., very high MPR (≥0.80);
   - **e** Without information on the number of days prescribed, thus missing information on compliance.

At the time of each NSAID prescription, the number of prescriptions, as well as the number, type and dosages of NSAIDs prescribed in the one year before were calculated approximating the prior exposure duration. Prescriptions with missing information on the expected duration of use were classified into a separate category.

Outcomes

The outcome of interest in this study was a first record of an upper GI event during follow-up; this could be based on a GP diagnosis or on a hospital or consultant letter as recorded by the GP. Upper GI events included gastroduodenal ulcers which were clinically symptomatic and ulcer complications, such as upper GI haemorrhage. Several independent studies show completeness of medical diagnoses and high degrees of validity of the CPRD database.[22-24]

Data analysis

Descriptive analyses were performed on the exposure characteristics of nsNSAIDs and coxibs in the two groups of interest, i.e. aged 65–74 years and ≥75 years. Incidence rates of upper GI events were estimated for all patients (SAS 9.2). Person-years of follow-up were computed by adding up all person-time from the start date to either the date of upper GI event or to the date of censoring, if no upper GI event had occurred. The incidence rate of upper GI events was defined as the number of events per 1,000 person-years.

Incidence rates of upper GI events were compared with those reported in published RCTs as obtained through a MEDLINE search with the following characteristics: English language, large RCTs (including ≥2,000 patients) or meta-analyses of RCTs with prevention of upper GI events as primary outcome, comparing coxibs with nsNSAIDs, and incidence rates of upper GI events as outcome measure.

Results

In table 1, the main characteristics of the two age group 65–74 years and ≥75 years in the study, stratified for nsNSAID and coxibs use, are summarised. Follow-up times of the individual groups were essentially similar (median 5.1 years; IQR 6.7 years). The majority of patients were female and, as expected, the number of risk factors for upper GI events was higher in the coxibs group, particularly in those patients 75 years or older. All four groups showed high frequencies of comorbidities and use of concomitant medicines.

In table 2, incidence rates of upper GI events for the two age classes (65-74 and ≥75 years) across different exposure categories are presented. The incidence rates of upper GI events were highest in first-time users, as well as in patients using their nsNSAIDs or coxibs on a daily basis for less than 6 months. In patients prescribed NSAIDs on a quarterly, monthly, or weekly basis, the incidence rates were lowest.

TABLE 1 Patients' characteristics at index date

Characteristic	nsNSAID, 65-74 y n=435,007	nsNSAID, ≥75 y n=214,134	Coxib, 65–74 y n=36,550	Coxib, ≥75 y n=28,533
Mean age (SD), y	68.0 (2.9)	81.0 (5.0)	68.3 (3.1)	81.7 (5.2)
Female, %	53.8	62.2	62.8	69.3
Upper GI risk factors, %				
0	26.3	16.0	17.2	11.2
1	20.9	17.0	20.4	15.2
2–4	39.9	46.9	44.5	49.3
≥5	12.9	20.1	17.9	24.3
Concomitant medication*, %				
Antihypertensive agents	42.8	56.3	48.2	61.3
Gastroprotective agents	21.9	24.1	31.5	29.7
Aspirin	18.0	27.0	20.6	30.5
Other anticoagulant agents	17.8	26.6	21.4	31.8
Oral glucocorticosteroids	3.5	4.6	5.7	6.4
Warfarin	1.0	1.9	1.9	3.2
Medical history, %				
Hypertension	36.1	42.4	37.8	43.7
Osteoarthritis	29.1	33.5	37.5	39.1
Ischemic heart disease	13.2	20.3	16.4	22.6
Diabetes mellitus	9.4	9.3	10.3	9.4
Chronic renal dysfunction	3.6	6.6	2.4	3.1
Peptic ulcer family history†	3.7	4.3	7.2	6.5
Heart failure	1.9	7.8	2.5	8.3
Rheumatoid arthritis	2.6	2.2	4.8	3.4
Upper GI bleed	1.0	1.5	1.9	2.4
History of bleeding	0	0.1	0.1	0.1
Medication use, %				
Ibuprofen	37.9	45.4	–	–
Diclofenac	37.5	31.9	–	–
Naproxen	13.3	9.9	–	–
Meloxicam	3.6	4.6	–	–
Celecoxib	–	–	44.7	46.2
Rofecoxib	–	–	36.9	41.9
Etoricoxib	–	–	17.5	11.1
Other	7.7	8.2	0.9	0.8

* Antihypertensive agents: β-receptor blocking sympathicolytic drugs, diuretic drugs, ACE inhibitors, calcium channel blocking drugs, selective α1-receptor blocking sympathicolytic drugs, centrally acting antihypertensive drugs, directly acting vasodilators, combinations of above-mentioned drugs. Gastroprotective agents: cimetidine, cimetidine/alginate, famotidine, nizatidine, ranitidine bismuth citrate, ranitidine hydrochloride, bismuth chelate, sucralfate, tripotassium dicitratobismuthate, PPIs. Other anticoagulant agents: aspirin, clopidogrel, dipyridamole, ticlopidine hydrochloride, dipyridamole/aspirin, abciximab, eptifibatide, prasugrel, ticagrelor. Oral glucocorticosteroids: budesonide, hydrocortisone acetate, hydrocortisone, prednisolone, prednisolone sodium metasulphobenzoate, prednisolone sodium phosphate, beclometasone dipropionate (systemic). † Peptic ulcer in family history: ICD codes in first degree family members.

TABLE 2 Distribution of prescription patterns of nsNSAIDs and coxibs and absolute risks of upper GI events

Prescription pattern	Proportion of current users	Incidence rate (per 1,000 py) 65-74 ys	Incidence rate (per 1,000 py) ≥75 ys
Non-selective NSAIDs			
Starters	14.3	3.2 (2.6–3.9)	7.3 (6.3–8.5)
Continuous users			
Quarterly use	14.8	1.9 (1.7–2.2)	3.4 (3.0–3.9)
Monthly use	12.9	1.5 (1.3–1.8)	3.4 (2.9–3.9)
Weekly use	11.8	2.5 (2.1–2.9)	4.5 (3.8–5.2)
Daily use	28.1	2.4 (2.2–2.7)	5.7 (5.4–6.1)
<6 mo	13.6	2.6 (2.1–3.0)	7.6 (6.7–8.5)
6–11 mo	9.8	2.4 (2.1–2.7)	4.8 (4.3–5.3)
All year	4.7	2.5 (2.1–2.9)	5.8 (5.2–6.4)
Coxibs			
Starters	8.4	3.1 (1.4–6.2)	8.3 (5.4–12.3)
Continuous users			
Quarterly use	12.2	2.4 (1.4–4.0)	3.3 (2.0–5.1)
Monthly use	12.4	1.5 (0.7–2.7)	6.3 (4.5–8.6)
Weekly use	13.3	2.4 (1.4–3.9)	4.7 (3.1–6.7)
Daily use	38.1	3.3 (2.7–3.9)	6.3 (5.5–7.2)
<6 mo	16.8	2.9 (1.9–4.4)	7.4 (5.7–9.5)
6–11 mo	14.1	3.4 (2.6–4.5)	6.1 (4.9–7.5)
All year	7.2	3.3 (2.4–4.6)	5.8 (4.5–7.2)

The upper GI risks did not differ substantially between nsNSAID and coxibs users. A clear and consistent age effect was seen in virtually all exposure categories. Incidence rates were highest for patients aged ≥75 years on a first nsNSAID prescription (IR 7.3 [95% confidence interval 6.3–8.5]), and during daily use (IR 5.7 [95%CI 5.4–6.1]). A similar age effect was seen in coxib users. Especially starters (IR 8.3 [95%CI 5.4–12.3]) and daily users (IR 6.3 [95%CI 5.5–7.2]) aged ≥75 years showed higher incidence rates than in the younger age group.

Comparison with RCTs

Eleven RCTs and meta-analyses of RCTs fulfilled the selection criteria (table 3).[11,16-20,25-29] The results of two studies were combined in two aspects; the first was a subgroup analysis of older participants of a larger RCT[20,25], the second was a pooled analysis that was updated five years later on the same set, combined with additional data.[19,27] The published trials reflected a study population of 114,739, compared with 714,224 patients in the CPRD cohort. Coxibs included in the RCTs were rofecoxib, celecoxib, etoricoxib, and lumiracoxib, which were compared with nsNSAIDs in high daily doses, most frequently diclofenac 150 mg, ibuprofen 2,400 mg, and naproxen 1,000 mg. Comparison of the frequency of upper GI events in the medical history did not vary greatly between RCT subjects (4.9%–13.4%), but was higher than in the CPRD cohort (nsNSAIDs 1.2% and coxibs 2.3%). The incidence rates of upper

TABLE 3 Characteristics of patients and NSAID exposure in the large RCTs or meta-analyses and in actual clinical practice (CPRD)

Study	Sample size	Daily Dose		Risk factors for upper GI events								Gastroprotective agents		Rate of upper GI events (per 1,000 py)	
				Age ≥75 years		Corticosteroid use		Aspirin use		History of upper GI events					
		coxib	nsNSAID	coxib	nsNSAID	coxib	nsNSAID	coxib	nsNSAID	coxib	nsNSAID	coxib	nsNSAID	coxib	nsNSAID
VIGOR, 2000 VIGOR subgroup analysis, 2002[20,25]	8,076	rofecoxib (50 mg)	naproxen (1,000 mg)			55.8	56.2			7.8	7.8	9.0	8.3	overall: 21 ≥75 ys: 45.1	overall: 45 ≥75 ys: 144.6
CLASS, 2000[11]	8,059	celecoxib (800 mg)	diclofenac (150 mg) ibuprofen (2,400 mg)	12	11	30.6	29.5	20.9	20.4	10.1	9.6	0	0	20.8	35.4
Ramey meta-analysis, 2005[17]	5,441	etoricoxib (60–120 mg)	diclofenac (150 mg) ibuprofen (2,400 mg) naproxen (1,000 mg)			27.3	26.7	3.8	4.5	6.5	6.9	11.5	13.0	10	24.7
Goldstein pooled analysis, 2004[28]	6,470	Valdecoxib (20–160 mg)	diclofenac (150 mg) ibuprofen (2,400 mg) naproxen (1,000 mg)	7.7	8.6	23.3	21.1	13.4	14.0	10.8	12.3			6.8	19.5
Langman meta-analysis, 1999 Watson meta-analysis, 2004[19,27]	17,072	rofecoxib (5–50 mg)	diclofenac (150 mg) diclofenac /misoprostol (100 mg/400 µg) ibuprofen (2,400 mg) nabumetone (1,500 mg) naproxen (1,000 mg)			10.4	7.4	6.3	8.3	6.7	5.4			7.4	18.7
Goldstein meta-analysis, 2000[26]	9,144	celecoxib (50-800 mg)	diclofenac (100–150 mg) ibuprofen (2,400 mg) naproxen (1,000 mg)	10	9.6	13.5	13.1	12.4	10.5	13.2	13.4	16.5	14.7	2.0	16.8
TARGET, 2004[29]	18,325	lumiracoxib (400 mg)	ibuprofen (2,400 mg) naproxen (1,000 mg)	10.7	10.9			23.8	23.7			0	0	4.2	12.5
MEDAL, 2007[16]	34,701	etoricoxib (60–90 mg)	diclofenac (150 mg)	11.7	11.0	15.4	15.7	34.6	34.6	6.5	6.6	38.7	38.5	6.7	9.7
SUCCESS, 2006[18]	13,274	celecoxib (200–400 mg)	diclofenac (100 mg) naproxen (1,000 mg)	12.8	12.5	0	0	7.1	7.2	4.9	5.3	0	0	1	8
Actual clinical practice (CPRD)	714,224	Heterogeneous	Heterogeneous	44	33	6.0	3.9	25.0	20.9	2.3	1.2	30.7	22.7	4.3	3.3

GI events during coxib use varied between 1 and 21/1,000 person-years (CPRD cohort 4.3), compared with incidence rates during nsNSAID use ranging from 8 and 45/1,000 person-years (CPRD cohort 3.3). One study reported the incidence rates of upper GI events in trial subjects aged ≥75 years, which was 45.1/1,000 person-years for coxib users, and 144.6/1,000 person-years in nsNSAID users. For this age group, the IRs for coxib users was at most 8.3/1,000 person-years (95%CI 5.4-12.3), and at most 7.6/1,000 person-years (95%CI 6.7–8.5) in nsNSAID users (table 2). As a result, the differences in IRs in nsNSAID users varied between 2.5 and 13.5 times higher in RCTs compared with daily practice, and in subjects aged ≥75 years 19 times higher. For coxib users, the IRs found in RCTs were 4 times lower to 5 times higher, even for those aged ≥75 years.

Discussion

In this study, a total of 714,224 NSAID users, stratified for age 65-74 and ≥75 years, and for nsNSAID and coxibs use, were studied regarding upper GI risk effect across different exposure categories. The highest incidence rates, 7.6/1,000 person-years for nsNSAID users and 8.3/1,000 person-years in coxib users, were found in patients aged 75 years or older. We found that risk of upper GI events across age and exposure groups in daily practice were much lower than in RCTs. The differences were largest in nsNSAID users, with IRs between 2.5 and 19 times higher in RCTs compared with daily practice. The IRs of upper GI events in coxib users were less disproportionate, namely at most 5 times higher, even for those aged ≥75 years.

The CPRD cohort differed from the RCTs in several aspects. First, most RCTs applied inclusion criteria stating that subjects were expected to require treatment for ≥6 months, up to one year, on a daily basis. Only 28.1% of nsNSAID users and 38.1% of coxib users in the CPRD cohort used the medication on a daily basis. Second, the proportion of participants aged ≥75 years was, if reported, much lower than in the CPRD cohort. However, based on the fact that increasing age is associated with a higher risk of upper GI events, the IRs found in the CPRD cohort would have been expected to be higher. Third, the proportion of corticosteroid use in the RCTs was, if allowed, roughly 2 to 14 times higher than in the CPRD cohort; aspirin users were mostly more frequent in the CPRD cohort, and a history of upper GI events was more frequently present in the RCT population. Fourth, whereas the diagnoses of upper GI events in the majority of the RCTs were confirmed by endoscopy or X-rays, this might not have been done in all CPRD patients. These factors probably have influenced the IRs of upper GI events.

It is possible that the lack of a protective effect of coxibs in daily practice is due to the phenomenon of channelling. Patients at a relatively high risk of upper GI events are more likely to be selectively prescribed coxibs instead of nsNSAIDs, a phenomenon described before in NSAID use.[30-34] In this study, channelling might have played a role; coxib users were older than nsNSAID users, had more upper GI risk factors, more frequently reported upper GI events in their family history, and used gastroprotective agents more often than nsNSAID users, while the IRs appeared to be comparable.

The IRs found in the CPRD cohort were higher in first time users and in daily users of nsNSAIDs compared with intermittent users, a finding reported before.[35] It is possible that this effect is due to "depletion of susceptibles".[36] NSAID users that experience an upper GI event will discontinue the drug, meaning that patients who continue NSAIDs are at a lower risk of upper GI events and have lower IRs. An important finding, however, is that the incidence of upper GI events was high in patients on their first prescription, especially in patients aged ≥75 years.

The inclusion of more than 714,000 patients in daily practice gives a thorough overview of the risk in real-life users of nsNSAIDs and coxibs. Especially the large proportion of patients aged 75 years or older provides new knowledge, since this population is included in RCTs to a limited extent. In addition, the median follow-up time of more than 5 years adds to the value of the study findings. Several independent studies revealed that the medical data in the CPRD database are generally of high quality.[22-24] It should be taken into account that patient exposure was based on prescription information rather than on actual use. Furthermore, some NSAIDs are available over-the-counter (OTC). OTC use is rarely recorded by general practitioners. Therefore, patients might have been on a prescription NSAID as well as an OTC NSAID. This may have led to misclassification of past or recent users and to an additional effect of multiple NSAID use on the risk of upper GI events. However, medications as obtained through the GP are free for patients aged 65 years or older; thus, older patients may be less likely to use OTC medication for chronic use.

Because of these strengths, this study is able to confirm findings of previous, often smaller, studies.[33,37,38] In some of these studies, the use of gastroprotective agents was very frequent (up to 60% of participants)[34], whereas the use of those medicines is frequently not allowed in RCTs. In this study, however, the use of gastroprotective agents was less frequent (at most 30% of participants), and more comparable to the included RCTs (0–39% of participants). As a result, the IRs could have been expected to be more comparable, but they were not. The difference in risk of upper GI events during NSAID use between real life and clinical trials was also found in other comparisons between these settings.[39,40]

Several findings of this study should be taken into account. First, the study shows that older people experience upper GI events during nsNSAID as well as during coxib use; a finding reported before.[41] In addition, increasing age above the age of 75 years appeared to be a risk factor for peptic ulcers, as shown in other studies.[42-44] In the CPRD cohort, the IRs during the first prescription, which is mostly one to three months, was high. Previous research suggested that the risk of upper GI events increases with nsNSAID treatment duration, with a maximum risk at 50 days of treatment.[45] This finding was based on the linear increase of IRs found in RCTs.

In conclusion, older patients using nsNSAIDs and coxibs showed overall lower frequencies of upper GI events in general practice than has been suggested by findings in RCTs. However, reported rates in RCTs varied highly and our research findings may be affected by differences in baseline risks of the studied populations and in the way GI events were diagnosed, classified and quantified in CPRD compared to RCTs. Observational studies in daily

practice, also as part of post-authorisation safety studies[46], remain important to add insight to what has been learned about certain drug-induced harms from RCTs. Undoubtedly, very old people are at higher risk of upper GI harm when taking NSAIDs, but RCTs alone are probably not the best resource to guide medical practice, and prescribing policies in particular. The contrast between what is found about upper GI risk in general practice and RCTs remains striking, albeit methodological factors may partly explain these differences. This study warrants further synergy between the different methods and data sources to evaluate drug-induced harm and to fuel risk mitigation policies accordingly. Evidence-based pharmacotherapy for older people deserves more than only RCT data.

References

1. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011; 171(6):550-6.
2. Bugeja G, Kumar A, Banerjee AK. Exclusion of elderly people from clinical research: A descriptive study of published reports. *BMJ* 1997; 315(7115):1059.
3. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomised controlled trials published in high-impact general medical journals: A systematic sampling review. *JAMA* 2007; 297(11):1233-40.
4. Uijen AA, Bakx JC, Mokkink HG, van Weel C. Hypertension patients participating in trials differ in many aspects from patients treated in general practices. *J Clin Epidemiol* 2007; 60(4):330-5.
5. Dowd R, Recker RR, Heaney RP. Study subjects and ordinary patients. *Osteoporos Int* 2000; 11(6):533-6.
6. Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry* 2002; 159(3):469-73.
7. McMurdo M. Clinical research must include more older people. *BMJ* 2013; 346:f3899.
8. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med* 2008; 168(17):1890-6.
9. Carrasco-Garrido P, de Andres LA, Barrera VH, de Miguel GA, Jimenez-Garcia R. Trends of adverse drug reactions related-hospitalizations in Spain (2001-2006). *BMC Health Serv Res* 2010; 10:287.
10. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; 329(7456):15-9.
11. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: The CLASS study: A randomised controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000; 284(10):1247-55.
12. Chan FK, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): A randomised trial. *Lancet* 2010; 376(9736):173-9.
13. Krueger K, Lino L, Dore R, Radominski S, Zhang Y, Kaur A, et al. Gastrointestinal tolerability of etoricoxib in rheumatoid arthritis patients: Results of the etoricoxib vs diclofenac sodium gastrointestinal tolerability and effectiveness trial (EDGE-II). *Ann Rheum Dis* 2008; 67(3):315-22.
14. Lanas A, García-Rodríguez LA, Arroyo MT, Gomollón F, Feu F, González-Pérez A, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut* 2006; 55(12):1731-8.
15. Lai KC, Chu KM, Hui WM, Wong BC, Hu WH, Wong WM, et al. Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications. *Am J Med* 2005; 118(11):1271-8.
16. Laine L, Curtis SP, Cryer B, Kaur A, Cannon CP, MEDAL Steering Committee. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the multinational etoricoxib and diclofenac arthritis long-term (MEDAL) programme: A randomised comparison. *Lancet* 2007; 369(9560):465-73.
17. Ramey DR, Watson DJ, Yu C, Bolognese JA, Curtis SP, Reicin AS. The incidence of upper gastrointestinal adverse events in clinical trials of etoricoxib vs. non-selective NSAIDs: An updated combined analysis. *Curr Med Res Opin* 2005; 21(5):715-22.
18. Singh G, Fort JG, Goldstein JL, Levy RA, Hanrahan PS, Bello AE, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I study. *Am J Med* 2006; 119(3):255-66.

19. Watson DJ, Yu Q, Bolognese JA, Reicin AS, Simon TJ. The upper gastrointestinal safety of rofecoxib vs. NSAIDs: An updated combined analysis. *Curr Med Res Opin*.2004; 20(10):1539-48.
20. Laine L, Bombardier C, Hawkey CJ, Davis B, Shapiro D, Brett C, et al. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: Results of a double-blind outcomes study in patients with rheumatoid arthritis. *Gastroenterology* 2002; 123(4):1006-12.
21. Van Staa TP, Leufkens HG, Zhang B, Smeeth L. A comparison of cost effectiveness using data from randomised trials or actual clinical practice: Selective cox-2 inhibitors as an example. *PLoS Med* 2009; 6(12):e1000194.
22. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the general practice research database: A systematic review. *Br J Clin Pharmacol* 2010; 69(1):4-14.
23. Walley T, Mantgani A. The UK general practice research database. *Lancet* 1997; 350(9084):1097-9.
24. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the general practice research database: A systematic review. *Br J Gen Pract* 2010; 60(572):e128-36.
25. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR study group. *N Engl J Med* 2000; 343(21):1520-8.
26. Goldstein JL, Silverstein FE, Agrawal NM, Hubbard RC, Kaiser J, Maurath CJ, et al. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. *Am J Gastroenterol* 2000; 95(7):1681-90.
27. Langman MJ, Jensen DM, Watson DJ, Harper SE, Zhao PL, Quan H, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999; 282(20):1929-33.
28. Goldstein JL, Eisen GM, Agrawal N, Stenson WF, Kent JD, Verburg KM. Reduced incidence of upper gastrointestinal ulcer complications with the COX-2 selective inhibitor, valdecoxib. *Aliment Pharmacol Ther* 2004; 20(5):527-38.
29. Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the therapeutic arthritis research and gastrointestinal event trial (TARGET), reduction in ulcer complications: Randomised controlled trial. *Lancet* 2004; 364(9435):665-74.
30. Layton D, Souverein PC, Heerdink ER, Shakir SA, Egberts AC. Evaluation of risk profiles for gastrointestinal and cardiovascular adverse effects in nonselective NSAID and COX-2 inhibitor users: A cohort study using pharmacy dispensing data in the Netherlands. *Drug Saf* 2008; 31(2):143-58.
31. Leufkens HG, Urquhart J, Stricker BH, Bakker A, Petri H. Channelling of controlled release formulation of ketoprofen (oscorel) in patients with history of gastrointestinal problems. *J Epidemiol Community Health* 1992; 46(4):428-32.
32. Martin RM, Biswas P, Mann RD. The incidence of adverse events and risk factors for upper gastrointestinal disorders associated with meloxicam use amongst 19,087 patients in general practice in England: Cohort study. *Br J Clin Pharmacol* 2000; 50(1):35-42.
33. MacDonald TM, Morant SV, Goldstein JL, Burke TA, Pettitt D. Channelling bias and the incidence of gastrointestinal haemorrhage in users of meloxicam, coxibs, and older, non-specific non-steroidal anti-inflammatory drugs. *Gut* 2003; 52(9):1265-70.
34. Depont F, Fourrier A, Merlière Y, Droz C, Amouretti M, Bégaud B, et al. Channelling of COX-2 inhibitors to patients at higher gastrointestinal risk but not at lower cardiovascular risk: The Cox2 inhibitors and tNSAIDs description of users (CADEUS) study. *Pharmacoepidemiol Drug Saf* 2007; 16(8):891-900.
35. Moride Y, Abenhaim L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. *J Clin Epidemiol* 1994; 47(7):731-7.

36. Miettinen OS, Caro JJ. Principles of nonexperimental assessment of excess risk, with special reference to adverse drug reactions. *J Clin Epidemiol* 1989; 42(4):325-31.

37. Czernichow P, Hochain P, Nousbaum JB, Raymond JM, Rudelli A, Dupas JL, et al. Epidemiology and course of acute upper gastro-intestinal haemorrhage in four French geographical areas. *Eur J Gastroenterol Hepatol* 2000; 12(2):175-81.

38. Laharie D, Droz-Perroteau C, Bénichou J, Amouretti M, Blin P, Bégaud B, et al. Hospitalizations for gastrointestinal and cardiovascular events in the CADEUS cohort of traditional or coxib NSAID users. *Br J Clin Pharmacol* 2010; 69(3):295-302.

39. Moore N. Comment on 'Quantitative estimation of rare adverse events which follow a biological progression: A new model applied to chronic NSAID use' Tramer et al., Pain 2000; 85:169-82. *Pain* 2001; 91(3):401-2.

40. Tramer MR, Moore RA, Reynolds DJ, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: A new model applied to chronic NSAID use. *Pain* 2000; 85(1-2):169-82.

41. Hippisley-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: Population based nested case-control analysis. *BMJ* 2005; 331(7528):1310-6.

42. Boers M, Tangelder MJ, van Ingen H, Fort JG, Goldstein JL. The rate of NSAID-induced endoscopic ulcers increases linearly but not exponentially with age: A pooled analysis of 12 randomised trials. *Ann Rheum Dis* 2007; 66(3):417-8.

43. Bardhan KD, Royston C. Time, change and peptic ulcer disease in Rotherham, UK. *Dig Liver Dis* 2008; 40(7):540-6.

44. Higham J, Kang JY, Majeed A. Recent trends in admissions and mortality due to peptic ulcer in England: Increasing frequency of haemorrhage among older subjects. *Gut* 2002; 50(4):460-4.

45. Richy F, Bruyere O, Ethgen O, Rabenda V, Bouvenot G, Audran M, et al. Time dependent risk of gastrointestinal complications induced by non-steroidal anti-inflammatory drug use: A consensus statement using a meta-analytic approach. *Ann Rheum Dis* 2004; 63(7):759-66.

46. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) – Module VIII – post-authorisation safety studies (EMA/813938/2011 Rev 1). (Accessed December 19, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf).

3.2

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatraemia associated with valproic acid

Four case reports from the Netherlands and a case/non-case analysis of Vigibase

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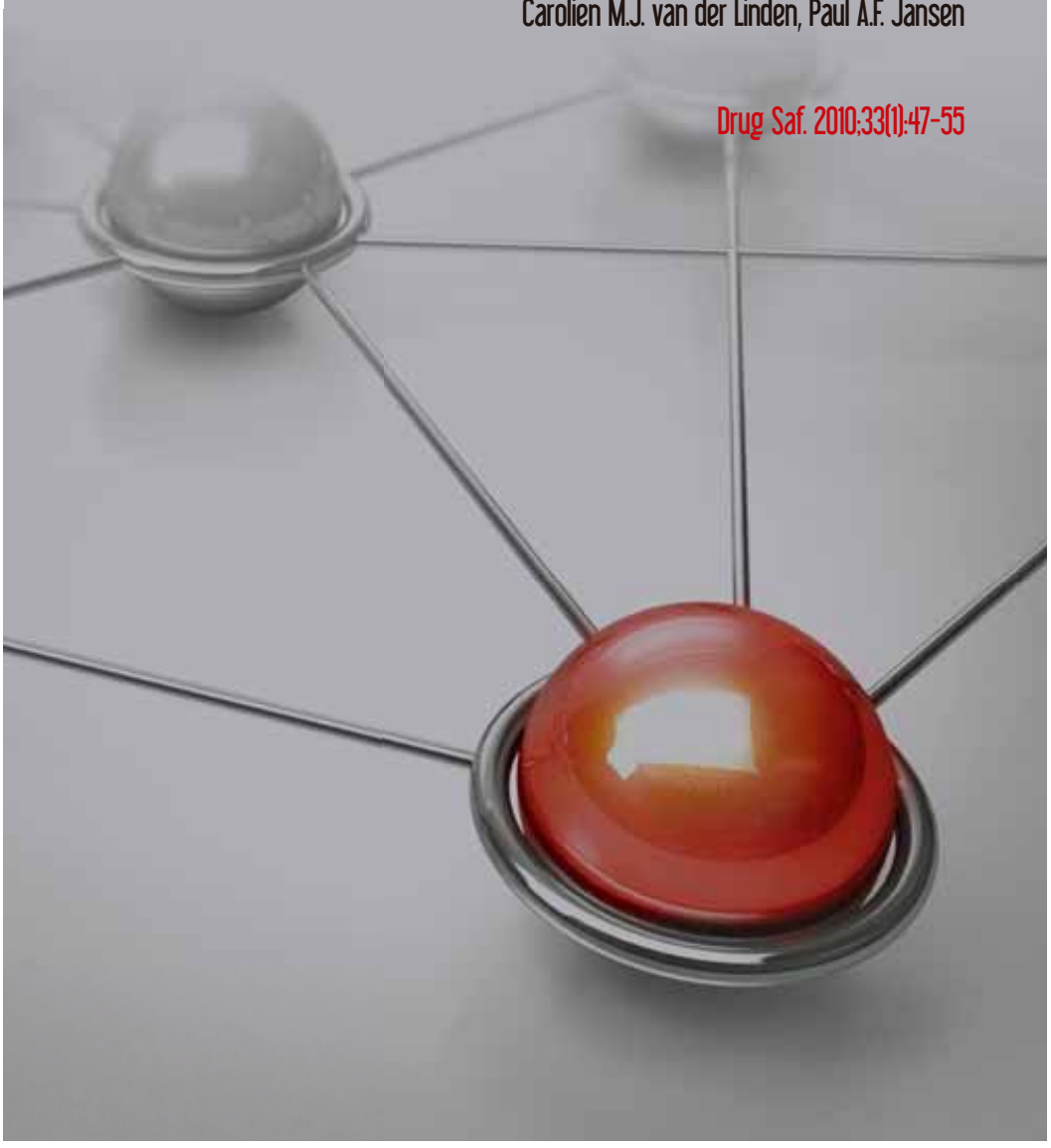


Abstract

Introduction The Netherlands Pharmacovigilance Centre Lareb received four cases of severe symptomatic hyponatraemia or syndrome of inappropriate antidiuretic hormone secretion (SIADH) in association with valproic acid use, in which a causal relationship was suspected. This study describes these cases and gives support for this association from Vigibase, the adverse drug reaction (ADR) database of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre.

Methods Cases of hyponatraemia in valproic acid users are described. In a case/non-case analysis, the strength of the association between reported cases of hyponatraemia and the use of valproic acid in Vigibase was established by calculating a reporting odds ratio, adjusted for possible confounding by concomitant medication.

Results Four females aged 57, 67, 71 and 88 years developed symptomatic hyponatraemia or SIADH after starting valproic acid. Despite concomitant medication or co-morbidity, a causal relationship was plausible. In Vigibase, valproic acid is disproportionally associated with hyponatraemia and SIADH (corrected reporting odds ratio 1.83 [95% confidence interval 1.61–2.08]).

Conclusions Based on the described cases and the reports from Vigibase, a causal relationship between valproic acid use and hyponatraemia or SIADH can be suspected. The mechanism by which valproic acid could cause hyponatraemia or SIADH has not been fully elucidated. Valproic acid use could lead to reduced sensitivity of hypothalamic osmoreceptors. It also might directly affect tubular cell function, thereby leading to SIADH. It might be expected that a combination of effects on the osmoreceptors and a lack of compensation of the salt-water unbalance by the nephrons causes SIADH in some patients using valproic acid. It could be a dose-or concentration-related adverse effect. In conclusion, in this report, severe symptomatic hyponatraemia and SIADH have been associated with the use of valproic acid. With this study, not only is the number of published cases doubled, but also the data from Vigibase strongly support the association. Since hyponatraemia and SIADH have a high morbidity, health professionals should be aware of this potential ADR.

Background

Hyponatraemia is defined as a serum sodium level of <135 mmol/L.[1,2] Mild hyponatraemia is generally asymptomatic, but serious symptoms occur if sodium levels fall below 125 mmol/L or when the condition develops rapidly (within 48 hours). Because of hypotonicity in the extracellular space, water flows into the cells and leads to cellular swelling and cerebral oedema. These effects result in early symptoms of headache, nausea, muscular weakness, lethargy, ataxia and confusion, which can progress to seizures, irreversible neurological damage, coma and death.[1–3]

Hyponatraemia can be due to impaired capacity of renal water excretion, effective arterial blood volume depletion, primary polydipsia, reset osmostat syndrome, hyperlipidaemia or hyper-paraproteinaemia.[4] Effective arterial blood volume depletion can be caused by several factors, for example vomiting, peritonitis, renal failure and the use of several drugs such as antidiuretic hormone (ADH) analogues, ADH-release agonists, or agents potentiating the action of ADH.[4,5] Hyponatraemia has also been associated with the use of antipsychotic drugs, antidepressants, certain anti-cancer agents and with several anti-epileptic drugs.[1,5–12]

In the syndrome of inappropriate ADH secretion (SIADH), the ADH arginine vasopressin (AVP) is released despite plasma hypo-osmolality, which is inappropriate. The syndrome is characterised by a euvolaemic hyponatraemia, with concentrated urine represented by an excessive urinary sodium concentration (>20 mmol/L) and urine hyperosmolality (>100 mOsmol/kg).[5] An excess of ADH can be found in SIADH, mineralocorticoid deficiency and hypothyroidism.[3,4] Laboratory parameters, such as thyroid function, cortisol level, serum and urine osmolality, urine levels of sodium,[4] as well as cerebral and thoracic imaging, are useful tests in the differential diagnosis of hyponatraemia.

Only four case reports in the literature describe hyponatraemia or SIADH as a possible adverse drug reaction (ADR) associated with use of the antiepileptic drug valproic acid.[13–16]

In this study we describe four cases of symptomatic hyponatraemia or SIADH in association with the use of valproic acid, which have been reported to the Netherlands Pharmacovigilance Centre Lareb. Because in the literature only four case reports were found, Vigibase, the database of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC), was also searched for the association.

Methods

The reports submitted to the Netherlands Pharmacovigilance Centre Lareb are described. Subsequently, the reports submitted to the WHO-UMC, are analysed. Currently, over 4.7 million ADR reports from more than 90 countries are filed in this database. One of the objectives of the WHO-UMC is to receive, analyse and record worldwide ADR data. ADRs are coded according to the WHO Adverse Drug Reaction Terminology. The suspected drugs are classified according to the WHO Drug Dictionary. For analysis purposes, the WHO Ana-

tomical Therapeutic Chemical (ATC) classification system, which is linked to the WHO Drug Dictionary, can be used. An ADR can be attributed to one or more suspected drugs and to one or more concomitant drugs.

All ADRs reported to the WHO-UMC until September 2007 were taken into account for this analysis. The index group consisted of reports with the suspected drug being valproic acid (ATC code N03AG01). The control group consisted of all other reports in the database. Cases were defined as reports mentioning the preferred terms 'hyponatraemia' or 'syndrome of inappropriate ADH secretion'. All other reports were selected as non-cases. The presence of suspected or concomitant drugs that have been associated in the literature with hyponatraemia was used as a co-variate (see table 1).[2]

The strength of the association between hyponatraemia and valproic acid compared with other drugs in the database was calculated using the ADR reporting odds ratio (ROR) as a measure of disproportionality.[17] Using the ROR, correction for co-variates can be easily made. An additional advantage is the fact that non-selective underreporting of a drug or ADR has no influence on the value of the ROR compared with the population of patients experiencing an ADR.[18] If more than four reports are received, the outcome of various methods is comparable. The Bayesian approaches are less likely to yield false positive results when low numbers (less than four reports) are involved. Given the high number of reports in this study, there is no reason to use this approach. In the present dataset, there is no advantage for using the proportional reporting ratio over the ROR or vice versa. Both methods yield similar results and are largely comparable.[18]

In this study we adjusted for the use of concomitant medication that had been associated with hyponatraemia in the past, calculated by means of logistic regression analysis and expressed as point estimates with corresponding 95% confidence intervals (CIs). In case the ROR is statistically significant, hyponatraemia is more frequently reported in association with valproic acid compared with the other drugs in the database.

Results

Cases

Patient A

Patient A is a 67-year-old female. Her medical history showed two myocardial infarctions, a cerebrovascular accident (CVA) in January 2005 and epilepsy following this CVA, for which she was treated with valproic acid (Depakine®) 500 mg twice daily since January 2005. She had never used valproic acid before. In the last year she did not experience epileptic seizures. Fourteen months after the start of valproic acid treatment, the patient was sent to hospital because of inability to walk without help for 2 weeks. She also had an insufficient intake of fluid and food, and occasionally signs of confusion for several days. Before the present admission, the serum sodium concentration was normal; the last sodium level was assessed in September 2005 (136–143 mmol/L).

TABLE 1 Suspected or concomitant drugs that have been associated with hyponatraemia

ATC code	name
A10BB02	chlorpropamide
C01BD01	amiodarone
C03A	'low-ceiling' diuretics, thiazides
C03C	'high-ceiling' diuretics
C07B	thiazides / beta blockers combination
C07D	thiazides and other diuretics / beta blockers combination
H01BA01	vasopressin
H01BA02	desmopressin
J01MA02	ciprofloxacin
L01AA01	cyclophosphamide
L01CA01	vinblastine
L01CA02	vincristine
L01XA01	cisplatin
N03AF01	carbamazepine
N03AF02	oxcarbazepine
N04BC01	bromocriptine
N05A	antipsychotics (without lithium N05AN)
N06A	antidepressants
N07BA01	nicotine

ATC Anatomical Therapeutic Chemical classification system.

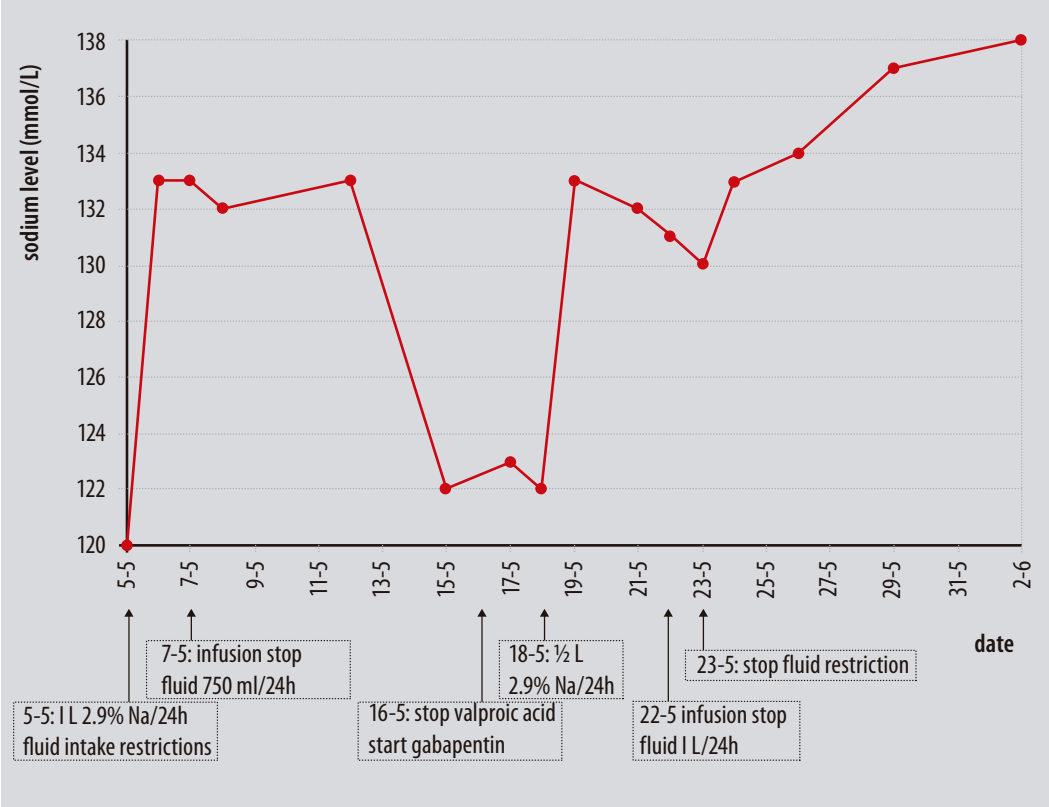
Laboratory findings on the day of admission and concomitant medications are shown in table 2. Other contributing factors besides the pre-existing CVAs were ruled out: nuclear MRI of the brain 1 week after admission revealed no pathology except ischaemic damage due to the CVA in 2005; a CT scan of the thorax revealed no relevant pulmonary pathology.

Sodium levels and actions taken are shown in figure 1. After normalization of the sodium level, this value remained stable and within the normal ranges (138–139 mmol/L).

Patient B

A 71-year-old female was admitted to the hospital because of hyponatraemia (125 mmol/L). She had a history of epilepsy and chronic leg pain due to a stenosis of the spine. A year before, she was also admitted because of hyponatraemia. During that admission, diuretic drugs were stopped. The effect of this cessation is unknown to the authors. Valproic acid and phenobarbital (phenobarbitone) were continued. At the present admission, her antiepileptic drugs were valproic acid 300 mg three times daily and phenobarbital 50 mg once daily. Concomitant medications are shown in table 2, as well as the relevant laboratory findings.

FIGURE 1 Sodium levels and actions undertaken in patient A



To rule out continued diuretic use, despite official cessation of the medication a year before, a drug screening in urine of diuretics was performed, which was negative. A urinary tract infection due to Escherichia coli was diagnosed. Thoracic x-ray was normal. An MRI of the lumbar spine revealed the known stenosis of the spine.

SIADH was diagnosed based on the laboratory findings and the absence of other causes for SIADH. During hospitalisation, the patient was treated with fluid restriction. The sodium level increased, but subsequently fell again to 124 mmol/L. Because other possible causes were ruled out, valproic acid was stopped, after which sodium level rose to 132 mmol/L. The patient was switched to topiramate to treat her epilepsy. She recovered fully and the concomitant medication was continued.

Patient C

An 88-year-old female was admitted to hospital because of sudden somnolence on the day of admittance. For about 2 days she experienced malaise, nausea and vomiting, and a weight loss of 4 kg in about 10 days was reported. She also had abdominal pain in the left lower quadrant. The patient had a history of asthma, epilepsy, hypothyroidism and cholecystectomy.

She was prescribed valproic acid 300 mg daily and phenobarbital 50 mg twice daily. Concomitant medication and laboratory findings are shown in table 2. Her thyroid function was normal. Neither x-rays of the thorax and abdomen, nor abdominal echography or laboratory findings revealed other pathology. Gastroscopy revealed a diaphragmatic hernia. Colonoscopy showed a diverticulosis, without signs of inflammation or other further pathology. SIADH was diagnosed.

During admission the somnolence disappeared spontaneously. The sodium level increased to 125 mmol/L within a few days and then did not change any further, although vomiting had stopped. Because other causes for the hyponatraemia were ruled out, it was suspected that valproic acid might have caused the SIADH, with a latency of 2 years. Valproic acid treatment was therefore stopped. In the following days, sodium level normalised and remained constant. Concomitant medication was continued. An explanation for the abdominal complaints was not found, but these might have worsened the hyponatraemia.

Patient D

A 57-year-old female was admitted to hospital because of symptoms of confusion, memory impairment, increasing somnolence and severe hyponatraemia. She had a history of multiple sclerosis since the age of 46 years and epilepsy since the age of 56 years. Her antiepileptic drugs were lamotrigine 200 mg daily and valproic acid 1000 mg twice daily. Because of an insufficient effect on convulsion frequency, the lamotrigine had been started in place of phenytoin about 5 months before the admission. Valproic acid dose was not changed. The plasma level of valproic acid after cessation of phenytoin was within the therapeutic range. Concomitant medication and laboratory findings are shown in table 2.

During admission, the patient received extra salt, and fluid intake was restricted. Valproic acid dose was decreased to 1500 mg daily and the lamotrigine dose was not altered. The sodium level then increased to 133 mmol/L, despite continuation of diuretic treatment. The patient was discharged from the hospital.

Vigibase analysis

Until September 2007, a total of 22,606 reports with valproic acid as the suspect medication were received. Hyponatraemia as the suspected ADR was reported in 238 (1.05%) of the reports. Concomitant medication also associated with hyponatraemia was present in 123 reports of these cases. Results are shown in tables 3 and 4. Logistic regression analysis showed that, in Vigibase, valproic acid use is statistically significantly associated with hyponatraemia (ROR 2.40; 95%CI 2.11–2.73). The ROR corrected for the presence of concomitant medication associated with hyponatraemia is 1.83 (95%CI 1.61–2.08).

TABLE 2 Clinical data and laboratory findings

Data	Normal range	Patient A	Patient B	Patient C	Patient D
VPA dose		500 mg BID	300 mg TID	300 mg OD	1000 mg BID
Concomitant drugs		amlodipine 5mg OD aspirin 80mg OD fusidic acid cream 20mg/g metoprolol 25mg TID olmesartan 20mg OD ranitidine 150mg OD thiamine 100mg OD	carbasalate calcium 80 mg OD esomeprazole 40 mg OD atorvastatin 10 mg OD vitamin B complex ibuprofen 400 mg BID	dipyridamole/salicylic acid 25/500 mg BID oxazepam 10 mg BID losartan 50 mg OD levothyroxine 100 µg OD rabeprazole 20 mg OD salmeterol/fluticasone inhaler 50/250 µg BID tiotropium inhalation powder 18 µg OD	atenolol/chlorthalidone oxybutynin bisacodyl potassium chloride
VPA level	50–100 mg/L				89
Sodium	136–146 mmol/L	120	125	116	116
Serum osmolality	275–300 mOsm/kg	252	256	249	
Creatinine	70–100 µmol/L	58	83	66	
Urea	2.9–7.5 mmol/l	3.3		4.0	
GFR*	85–125 ml/min	76			
Urine sodium	130–200 mmol/24 h	46	94	28	
Urine osmolality	275–300 mmol/kg	562	286	224	
AVP	0.2–4.7 ng/L	0.37			
TSH	0.5–3.9 mU/l	1.9	2.3	3.37	
FT4	9–24 pmol/l	14	26	16	
Cortisol	0.15–0.70 nmol/l	0.64	0.66	0.26	

VPA valproic acid; GFR glomerular filtration rate; AVP arginine vasopressin; * calculated with Cockroft-Gault formula

TABLE 3 Figures from Vigibase — reports in which concomitant medication associated with hyponatraemia or syndrome of inappropriate antidiuretic hormone secretion (SIADH) was present

	VPA present	VPA absent
hyponatremia or SIADH present	123	10,806
hyponatremia or SIADH absent	7,349	787,554

VPA valproic acid

TABLE 4 Figures from Vigibase — reports in which concomitant medication associated with hyponatraemia or syndrome of inappropriate antidiuretic hormone secretion (SIADH) was absent

	VPA present	VPA absent
hyponatremia or SIADH present	115	6,139
hyponatremia or SIADH absent	15,019	3.039,982

VPA valproic acid

Discussion

This study describes four patients who developed severe symptomatic hyponatraemia or SIADH requiring hospital admission, strongly suggestive of a causal relationship with the use of valproic acid. The data from Vigibase support this association.

Our study has its limitations. First, the described cases are derived from a spontaneous reporting system. The information given by the reporter can be limited, for example on reaction outcome or on the patient's health status prior to the adverse event (e.g. fluid intake prior to the occurrence of hyponatraemia). To assess causality between the suspect drug and the reported adverse event, additional information is often needed, but not always provided.

Second, the patients used concomitant medication that has been associated with hyponatraemia. They also had other risk factors for the development of hyponatraemia. Furthermore, sodium level can normalise following fluid intake restriction or even without intervention. Taking these considerations into account, we considered the hyponatraemia in the described patients as probably due to valproic acid use. In patient A, all risk factors for hyponatraemia, except the cerebrovascular accident 14 months before, were ruled out. This patient only fully recovered after cessation of valproic acid.

Patient B was administered ibuprofen as concomitant medication. Hyponatraemia has been rarely described with the administration of ibuprofen.[19,20] Because the sodium level rose to 132 mmol/L after cessation of valproic acid, while ibuprofen was continued, a causal relationship with the valproic acid was considered the most plausible. Patient C concomitantly used losartan. Hyponatraemia has been reported during the post-marketing use of losartan,[21] but has not been reported in literature. However, she experienced vomiting at hospital admission and this can be either a risk factor for hyponatraemia, or a consequence of it. Her concomitant medicines (table 2) also included levothyroxine sodium: hypothyroidism, the indication for levothyroxine sodium use, is associated with hyponatraemia. Plasma levels of thyroid function parameters were normal in patient C. It is unclear what role the abdominal pain might have played in the hyponatraemia. A causal relationship between valproic acid use and hyponatraemia was suspected, because the sodium level only normalised after cessation of valproic acid, and other common causes for hyponatraemia were ruled out. Patient D used atenolol with chlortalidone. This thiazide-related sulfonamide has been previously associated with hyponatraemia.[22] The multiple sclerosis in this patient is also a risk factor for hyponatraemia and SIADH.[23–25] Her sodium level did rise, but did not normalise after dose decrease of valproic acid. The time relationship between valproic acid use and the occurrence of hyponatraemia, however, was suggestive of a causal relationship.

In cases originating from spontaneous reporting systems, not all information is available at time of reporting. For this reason, retrieving additional information is often needed, but not always are all clinical details provided, such as fluid intake prior to admission. Information on fluid intake was not provided in any of the cases.

Third, using Vigibase also has its shortcomings. The WHO-UMC collects ADR reports from over 90 countries. A known limitation of ADR databases is that they can include duplicate reports, leading to a statistically generated false signal if there are a high number of duplicates. Features about duplicate reports were not available to the authors. However, the role of duplicate reports does not play a significant role in this particular association, because the number of reports associating hyponatraemia to valproic acid is 238. Furthermore, the existence of duplicate reports has its influence on both the numerator and the denominator of the ROR. Only if the duplicate reports within the cases of valproic acid/hyponatraemia were higher compared with the other reports in the database, could an increase in the ROR be expected. We have no indication for this.

Using the ROR might not be familiar to readers. It is, however, a method used in the statistical approach of spontaneous reporting systems. One of the advantages of using the ROR is the possibility to correct for co-variates in logistic regression analysis. Moreover, the ROR is less sensitive for non-differential misclassification or under-reporting than other measures.[26]

Finally, to calculate the strength of the association between hyponatraemia and SIADH and valproic acid in Vigibase, as a co-variate we corrected for the presence of suspected or concomitant drugs that have been associated in the literature with hyponatraemia. We have limited our selection to the relatively common associated drugs in order to keep the calculation clinically relevant.

The mechanism by which valproic acid could cause hyponatraemia or SIADH has not been fully elucidated. SIADH due to drugs can be caused by stimulation of the release of ADH by the hypophysis, by enhancing ADH action on the kidney, by acting directly on the kidney, or by inhibiting the vasopressinase activity, resulting in prolonged vasopressin half-life.[7,11,14] The AVP level in patient A was within the normal range, but not suppressed. This was seen in patients with SIADH in the literature as well.[2,14,27] In one case report of a patient with hyponatraemia after treatment with valproic acid, AVP levels were low, but the AVP levels of this patient did not respond to water loading when combined with a high dose of valproic acid.[14] Another patient, however, showed an AVP increase to 14.1 pmol/L after treatment with valproic acid, which returned to normal after valproic acid was changed to another antiepileptic drug.[15]

Valproic acid could make hypothalamic osmo-receptors less sensitive, which was also suggested for carbamazepine and oxcarbazepine.[7,28] This could explain the inappropriate but inter-individually fluctuating ADH levels and the lack of response of AVP to water loading during valproic acid treatment, as described in the case reports.

The high AVP level during valproic acid treatment in one patient is more likely caused by a reaction of valproic acid on the renal tubular system, since the tubules do not seem to respond by reabsorbing sodium.[15] In children, valproic acid has shown to alter the renal tubular system, possibly leading to interference with kidney function, causing hypersensitive interstitial nephritis or Fanconi syndrome.[29,30] The effect of valproic acid on the renal tubular system suggests that it may directly affect tubular cell function, thereby causing SIADH.

Possibly a combination of effects on the osmoreceptors and a lack of compensation of the salt-water imbalance by the nephrons causes SIADH in some patients using valproic acid.[28]

Hyponatraemia due to valproic acid could be a dose-or concentration-related adverse effect. In two cases, the study of Branten *et al.*[14] and our case patient D, showed that a dose decrease of valproic acid resulted in less severe hyponatraemia.

Conclusions

This study describes hyponatraemia and SIADH as a possible ADR of valproic acid, based on four patients and support from Vigibase. This association between valproic acid use and hyponatraemia and SIADH has been recognised before. It is not yet described in all summaries of product characteristics worldwide. With this study, not only have the number of published cases doubled, but the data from the Vigibase strongly support the association.

Since hyponatraemia and SIADH have a high morbidity and mortality,[3] health professionals should be aware of this possible ADR associated with valproic acid. Electrolytes should be monitored closely during treatment with valproic acid in patients with risk factors for hyponatraemia or SIADH, such as the elderly.

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References

1. Palmer BF, Gates JR, Lader M. Causes and management of hyponatremia. *Ann Pharmacother* 2003; 37:1694–702.
2. Ellison DH, Berl T. Clinical practice: the syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; 356:2064–72.
3. Clayton JA, Le Jeune I, Hall IP. Severe hyponatraemia in medical in-patients: aetiology, assessment and outcome. *Q J Med* 2006; 99: 505–11.
4. Milionis HJ, Liamis GL, Elisaf MS. The hyponatremic patient: a systematic approach to laboratory diagnosis. *CMAJ* 2002; 166:1056–62.
5. Kumar S, Berl T. Sodium. *Lancet* 1998; 352:220–8.
6. Movig KL, Leufkens HG, Lenderink AW, van den Akker VG, Hodiamont PP, Goldschmidt HM, et al. Association between antidepressant drug use and hyponatraemia: a case-control study. *Br J Clin Pharmacol* 2002; 53:363–9.
7. Amelsvoort T van, Bakshi R, Devaux CB, et al. Hyponatremia associated with carbamazepine and oxcarbazepine therapy: a review. *Epilepsia* 1994; 35:181–8.
8. Kloster R, Borresen HC, Hoff-Olsen P. Sudden death in two patients with epilepsy and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). *Seizure* 1998; 7:419–20.
9. Cilli AS, Algun E. Oxcarbazepine-induced syndrome of inappropriate secretion of antidiuretic hormone. *J Clin Psychiatry* 2002; 63:742.
10. Nasrallah K, Silver B. Hyponatremia associated with repeated use of levetiracetam. *Epilepsia* 2005; 46:972–3.
11. Miller M. Hyponatremia and arginine vasopressin dysregulation: mechanisms, clinical consequences, and management. *J Am Geriatr Soc* 2006; 54:345–53.
12. Ma RC, Kong AP, Chan N, et al. Drug-induced endocrine and metabolic disorders. *Drug Saf* 2007; 30:215–45.
13. Ikeda K, Moriyasu H, Yasaka M, Oita J, Yamaguchi T. Valproate related syndrome of inappropriate secretion of antidiuretic hormone (SIADH): a case report. *Rinsho Shinkeigaku* 1994; 34:911–3.
14. Branten AJ, Wetzels JF, Weber AM, Koene RA. Hyponatremia due to sodium valproate. *Ann Neurol* 1998; 43:265–7.
15. Miyaoka T, Seno H, Itoga M, Kishi T, Ishino H, Horiguchi J. Contribution of sodium valproate to the syndrome of inappropriate secretion of antidiuretic hormone. *Int Clin Psychopharmacol* 2001; 16:59–61.
16. Herment N, Herlem E, Germain ML, Trenque T. [Hyponatremia induced by sodium valproate. A case report]. *Thérapie* 2006; 61:544–7.
17. Van Puijenbroek E, Diemont W, van Grootheest K. Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions. *Drug Saf* 2003; 26:293–301.
18. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf* 2002; 11:3-10.
19. Blum M, Aviram A. Ibuprofen induced hyponatraemia. *Rheumatol Rehabil* 1980; 19:258–9.
20. Rault RM. Case report: hyponatremia associated with nonsteroidal antiinflammatory drugs. *Am J Med Sci* 1993; 305:318–20.
21. FDA/Center for Drug Evaluation and Research. SmPC Cozaar®. (Accessed April 20, 2009, at http://www.fda.gov.proxy.library.uu.nl/cder/foi/label/2006/020386s045lbl.pdf).

22. Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced severe hyponatremia: review and analysis of 129 reported patients. *Chest* 1993; 103:601–6.

23. Sakai N, Miyajima H, Shimizu T, Arai K. Syndrome of inappropriate secretion of antidiuretic hormone associated with multiple sclerosis. *Intern Med* 1992; 31:463–6.

24. Liamis G, Elisaf M. Syndrome of inappropriate antidiuresis associated with multiple sclerosis. *J Neurol Sci* 2000; 172:38–40.

25. Nakasaka Y, Atsumi M, Saigoh K, Yamada A, Hirose N, Ishikawa K. [Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) associated with relapsing multiple sclerosis]. *No To Shinkei* 2005; 57:51–5.

26. Van der Heijden PG, van Puijenbroek EP, van Buuren S, van der Hofstede JW. On the assessment of adverse drug reactions from spontaneous reporting systems: the influence of underreporting on odds ratios. *Stat Med* 2002; 21:2027–44.

27. Robertson GL. Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. *Am J Med* 2006; 119:S36–42.

28. Gold PW, Robertson GL, Ballenger JC, Kaye W, Chen J, Rubinow DR, et al. Carbamazepine diminishes the sensitivity of the plasma arginine vasopressin response to osmotic stimulation. *J Clin Endocrinol Metab* 1983; 57:952–7.

29. Knorr M, Schaper J, Harjes M, Mayatepek E, Rosenbaum T. Fanconi syndrome caused by antiepileptic therapy with valproic acid. *Epilepsia* 2004; 45:868–71.

30. Watanabe T, Yoshikawa H, Yamazaki S, Abe Y, Abe T. Secondary renal Fanconi syndrome caused by valproate therapy. *Pediatr Nephrol* 2005; 20:814–7.

3.3

Practical problems with medication use experienced by older people

A qualitative study

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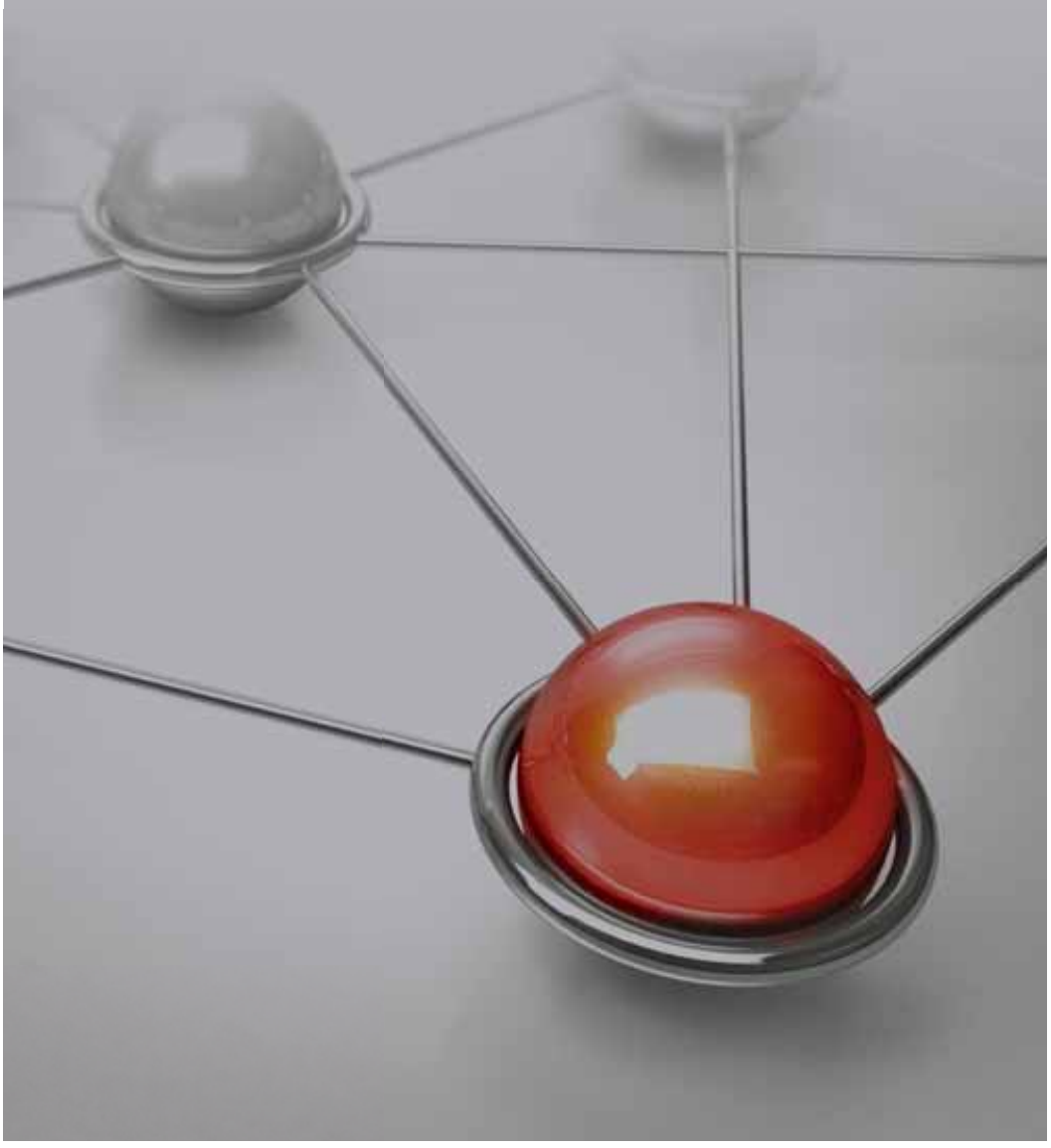


Abstract

Introduction This study aimed to identify the practical problems that older people experience when taking their medicines and how they manage these problems, and to determine the potential clinical relevance thereof.

Methods A qualitative study with semi-structured face-to-face interviews was performed in a community pharmacy and a geriatric outpatient ward in Utrecht, the Netherlands. Participants were 59 community-dwelling people aged 70 years or older who used at least three different oral prescription medicines daily and managed their medication independently.

Results A total of 211 practical problems and 184 strategies to manage these problems were identified. Fifty-six (95%) participants experienced one or more practical problem, ranging from problems with reading and understanding the instructions for use, handling the outer packaging, handling the immediate packaging, completing any preparation prior to use, and taking the medicine. In ten participants at least one of their problems, in combination with the strategy to resolve the problem, was considered to have potential clinical consequences, and eleven (5%) problems were considered to potentially cause moderate or severe clinical deterioration.

Conclusions Older people experience a number of problems using their medicines and these problems can lead to incorrect medication use, with potentially clinically relevant consequences. This study provides a classification of the practical problems experienced by older people. The findings challenge healthcare professionals, drug developers and regulators to find ways to diminish the practical problems experienced by older people.

Introduction

The therapeutic effect of medication is determined by its correct and timely use. Yet a number of steps are involved in taking medicines as recommended, such as reading and understanding the user information, opening and removing the medicine from the outer and immediate packaging, completing any preparation prior to use, and finally taking the medicine. Cognitive impairments and physical limitations, such as poor eyesight, weakness in the hands and fingers, loss of fine motor skills, or dysphagia, which increase with age, make it difficult to perform these actions.[1-5] Older people, therefore, tend to have more practical problems when using their medications than do younger people.[1-4, 6-9] Strategies to manage these practical problems, or a lack thereof, could negatively affect the correct and timely use of medicines, e.g., when doses are omitted because assistance is needed to open a container.[4, 10]

Little is known about the practical problems older people have when trying to take their medicines or the strategies they use to cope with these problems. A number of studies have investigated specific medicine handling problems, namely, opening medicine packaging[1, 9], breaking tablets[11], or a combination of specific problems, but none have investigated the complete sequence of actions that patients must undertake when taking medicine. Furthermore, most researchers have observed participants handling medication or packaging systems selected specially for the studies, but not their own medication packaging,[1, 3, 6, 9, 12, 13] Only a few studies have addressed the potential clinical consequences of the practical problems and the coping strategies.[4, 14, 15]

The aims of this study aims are to identify the practical problems that older people experience when taking medicine and the strategies they use to manage these problems, and to determine the potential clinical relevance of these problems and strategies.

Methods

Study design and recruitment

A qualitative study with semi-structured face-to-face interviews was performed. The participants were recruited from a community pharmacy belonging to the Utrecht Pharmacy Practice Network for Education and Research (UPPER) as well as from the geriatric outpatient ward of the University Medical Center Utrecht (UMCU), both in the Netherlands, between January 2011 and July 2012. A purposive sampling technique was chosen for data collection to ensure sufficient prevalence of a variety of problems with medicine use. Participants were eligible if they lived in the community, were 70 years or older, and used at least three different oral prescription medicines daily. Individuals were excluded if their medication was entirely managed by professional help or by the participant's carer, or if the medication was delivered in multi-compartment pillboxes or in other multi-dose dispensing systems.

Eligible people were approached by their community pharmacist or geriatrician. If willing to cooperate, they were provided with information about the study and were asked if they could agree to be contacted by a researcher (KN, EB, or an assistant) and whether their dispens-

ing record could be used for the study. Participants were recruited until data saturation was achieved, defined as no new practical problems with medication use and no new management strategies mentioned in five consecutive interviews.

Ethical considerations

This study was not subject to the Medical Research Involving Human Subjects Act (WMO), as confirmed by the UPPER institutional review board of the Department of Pharmacoepidemiology and Clinical Pharmacology (Utrecht University, the Netherlands) and by the medical ethics committee of the UMCU. The study was reviewed by and conducted in compliance with the requirements of the UPPER institutional review board (http://www.uu.nl/vkc/upper). Written informed consent was obtained from all participants before start of the interview. To protect the participants' privacy, a unique code for each participant was assigned to all medical, visual, and audio data.

Data collection

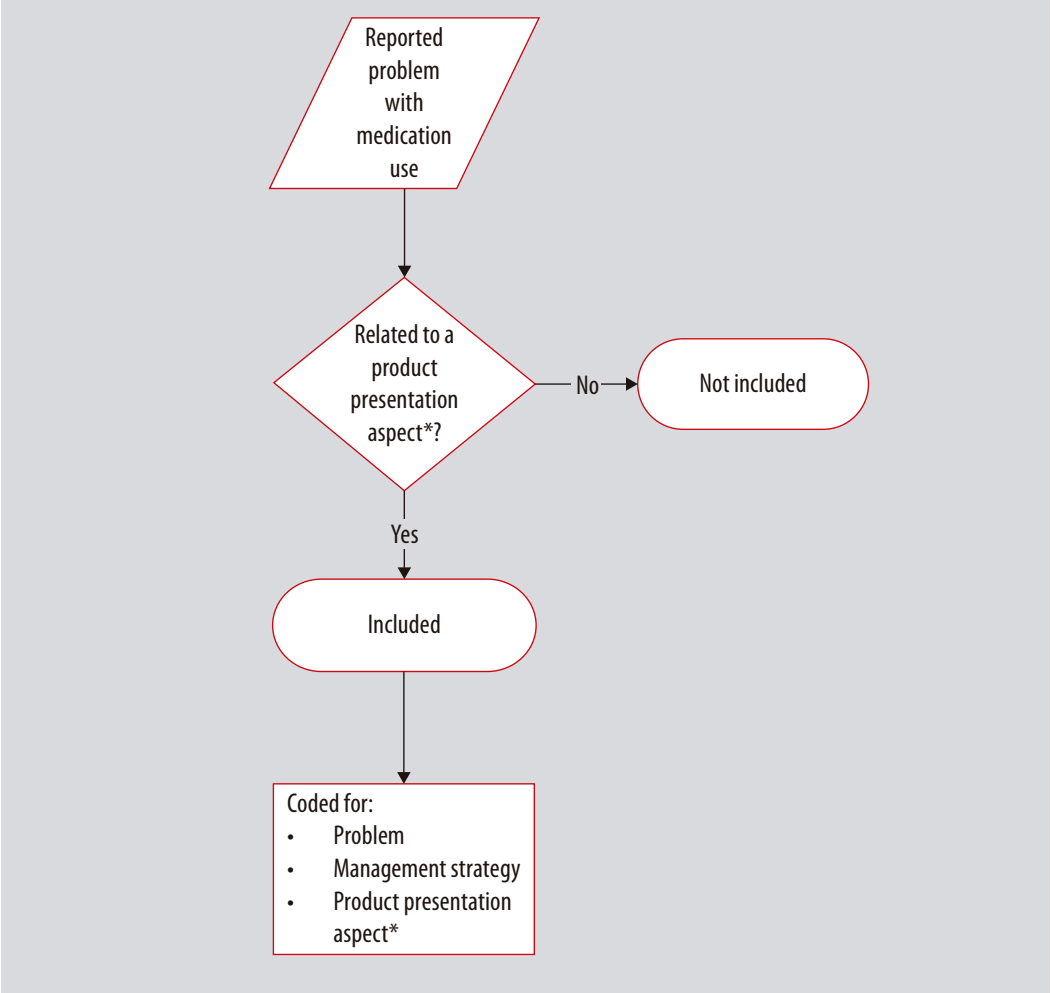
For the purposes of this study, practical problems with medication use were defined as problems related to the presentation (labelling and patient information leaflet, the material and type of outer and immediate packaging, and the administration device) and formulation (colour, shape, size, taste, surface texture, and any break mark on a medicine) of a medicine (figure 1). Problems related to personal preferences were not included; for example, the carton not fitting into the medicine cabinet because of its size.

The interviews were guided by a topic list (supplementary information) based on problems of medication use found in the literature. The participants were interviewed at home and could stop the interview at any time. Before being interviewed, the participants were asked to show the interviewer the medicines they used; these were checked against their pharmacy's dispensing record. Although the interview was recorded, field notes were taken to capture relevant information about the reported problems and the participants' management strategies. If appropriate, photographs of the medicines were taken to illustrate the problems experienced or management strategies. This information and preliminary interpretations formed during the interview were verified with the participants at the end of the interview. Interviews were conducted by two of five researchers experienced in healthcare and communication (KN, EB, CB, HL and MV).

Data processing, coding, and analysis

All interviews were recorded and transcribed verbatim. The transcripts were imported in ATLAS.ti software for coding and analysis (version 7.0, Scientific Software Development GmbH, Berlin, Germany). The reliability and validity of the transcribed data were ensured by the combination of voice-recording, notes, and visual material. The problems and the participants' management strategies were coded independently by KN (MSc pharmaceutical sciences) and EB (MD/clinical pharmacologist) according to a coding scheme (supplementary information) that was based on practical problems with medication use and management strategies reported in the literature.[2, 5, 8, 9, 12, 13, 16-24] The coding scheme was continuously updated during data analysis. The two researchers discussed disagreements in coding until consensus was reached. Another researcher (MLB, ACGE, or PAFJ) was con-

FIGURE 1 Flow chart of the inclusion of reported practical problems



* Labelling, patient information leaflet, the material and type of outer and immediate packaging, the colour, shape, coating, taste and size of the medicinal product, the score line of a tablet or a dosing device

sulted if consensus was not reached. Consistent coding was achieved by 'constant comparison'. Coding was done concurrently with the data collection process to evaluate data saturation.

An expert panel consisting of a community pharmacist (MLB), a hospital pharmacist (ACGE), and a clinical geriatrician/clinical pharmacologist (PAFJ) independently classified the potential clinical relevance of each practical problem and associated management strategy using the three-point scale developed by Cornish *et al.*[25] Class 1 relevance was defined as unlikely to cause patient discomfort or clinical deterioration, class 2 relevance as having the potential to cause moderate discomfort or clinical deterioration, and class 3 relevance as having the potential to result in severe discomfort or clinical deterioration. The potential clinical relevance was determined in relation to the medicine used. Disagreements in classification were resolved by discussion between the three researchers until consensus was reached.

Results

Fifty-nine people participated in this study. Their mean age was 78.4 years (SD 6.2; range 70-92), 38 (64.4%) were women, and 30 (50.8%) lived alone, 26 (44.1%) lived with a partner, and 3 (5.1%) lived with a relative. On average, participants used 6.9 prescribed oral medicines (SD 2.2; range 3-12). In total, 211 problems were reported, ranging from no problems in three participants to 14 problems in one participant; 184 management strategies were reported. While 94.8% (200 out of 211 problems) of the practical problems were not considered to result in discomfort or clinical deterioration (class 1), 3.3% (7 problems) of the problems were considered to potentially result in moderate discomfort or clinical deterioration (class 2) and 1.9% (4 problems) were considered to potentially result in severe discomfort or clinical deterioration (class 3). These 11 potentially clinically relevant problems were reported by 10 participants (17%). The problems experienced and the management strategies used are reported below, along with representative interview quotes. A classification of the practical problems is presented in figure 2.

Reading and understanding instructions for use

Of the 59 participants, 37 reported a total of 53 problems with reading and understanding the instructions for use (table 1). Most problems (n=24) concerned the description of adverse events in the patient information leaflet, which participants found distressing, so much so that 19 participants did not read the patient information leaflet (again), and three participants used a lower dose than prescribed or did not take the medicine at all. One participant regularly omitted doses of pantoprazole, which was considered to potentially result in severe discomfort or clinical deterioration due to an increased risk of gastric bleeding (table 2):

"After reading the instruction leaflet, I decided to limit myself to one tablet every two days. This is because I consider it harmful rubbish. You can expect all kinds of problems and the side effects are gigantic. I admit that I'm just a layperson and maybe you think I shouldn't get upset about this, but I wish I hadn't read the instruction leaflet. Yes, I do skip doses. The medicine is not as harmless as one thinks." (Male, 80 years, pantoprazole 20 mg)

Handling outer packaging

Seventeen participants reported a total of 19 problems with handling the outer packaging (table 1). Nine of these problems concerned opening the outer packaging – there were 5 reports of scissors or a knife being used to open the packaging.

"It seemed that at a certain moment the box became more difficult to open. Both ends were stuck down. This wasn't previously the case, so why are they stuck down now? I don't understand, is this to make life more difficult? You have to scratch it open with your fingernails but this is actually quite difficult. It would be better if the box just opened as it is supposed to."
(Male, 71 years, atorvastatin 20 mg)

Difficulties identifying medicines by their packaging were reported three times, and two participants wrote the therapeutic indication on the carton to avoid confusing boxes that looked alike. None of strategies used to overcome problems with the handling of the outer packaging were considered to have clinical consequences.

FIGURE 2 Overview of the main practical problems per medication-handling action

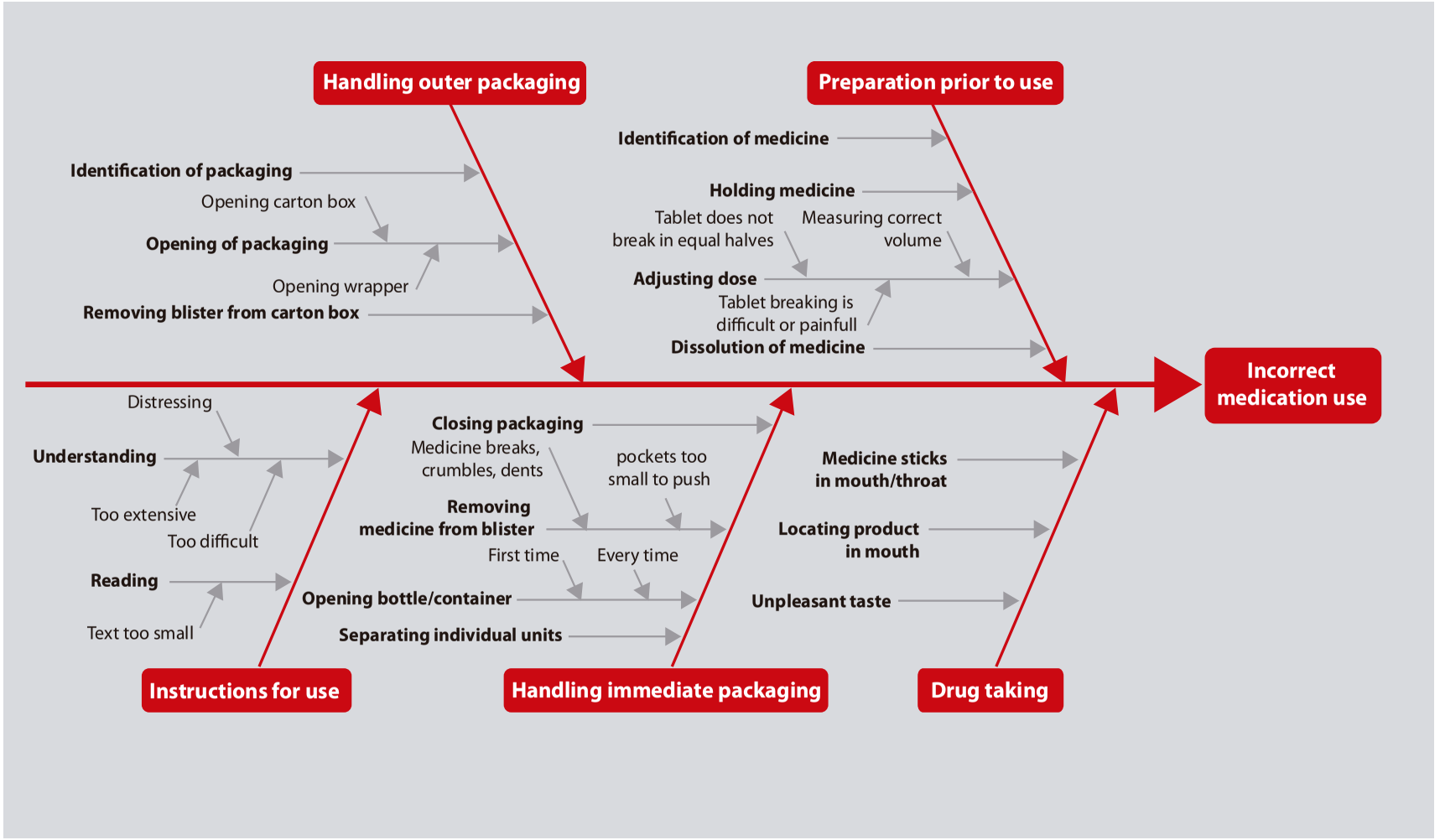


TABLE 1 Practical problems and related management strategies reported by the 59 participants

Practical problem	Management strategy
Reading and understanding instructions for use (n=53, by 37 participants)	
Text is too small (n=12)	No solution/Not reading package insert (regularly) (n=6), Use of magnifying glass (n=5), Use of extra light (n=1)
Information is too difficult (n=5)	No solution/Not reading package insert (regularly) (n=4), Read information on packaging (n=1)
Information is too extensive (n=12)	No solution/Not reading package insert (regularly) (n=12)
Information on adverse events is distressing (n=24)	Not reading patient information leaflet (regularly) (n=19), No solution (n=3), Using no or lower dose (n=3)
Handling of outer packaging (n=19, by 17 participants)	
Identification of product (n=3)	Writing on packaging (n=2), No solution (n=1)
Opening of packaging:	
Carton box (n=6)	Other way of opening (n=3), Using sharp equipment (n=3)
Wrapper around blister (n=3)	Using sharp equipment (n=2), No solution (n=1)
Removing blister from carton box (n=7)	Leave package insert away (n=7)
Handling of immediate packaging (n=73, by 38 participants)	
Separating individual units (sachets, vials, or blister cups) (n=9)	Using sharp equipment (n=5), No solution (n=2), using nails (n=1)
Opening of packaging:	
First time (n=13)	Assistance (n=6), Using sharp equipment (n=3), Using auxiliary aid (n=2), No solution (n=2)
Every time (n=7)	Not closing properly (n=4), Using other packaging (n=2), Assistance (n=1), Using sharp equipment (n=1), No solution (n=1), Push/twist with palm of hand (n=1)
Removing medicine from:	
Bottle (n=1)	Using other packaging (n=1)
Blister (n=42)	Using sharp equipment (n=8), No solution (n=6), Using nails (n=1), Change to packaging (n=1)
Medicine dents, opens, breaks or crumbles (n=15)	Administration of pieces (n=9), Take another dosage (n=2), Using nails (n=2), No solution (n=1)
Tearline tears instead of blister opening (n=4)	No solution (n=4)
Pockets too small to push (n=7)	Using nails (to push on pocket/open lidding foil) (n=6), Remove two tablets at once (n=1)
Pockets too large to localise product (n=1)	Using nails (n=1)
Closing packaging (n=1)	Removing stopper from cap (n=1)
Identification of medicine (n=10)	Store separate from look-alike medicine (n=5), Writing on immediate packaging (n=2), Reading embossment (n=1)
Holding medicine (n=12)	No solution (n=12)
Adjusting dose:	
Tablet breaking (n=9)	
Difficult/painful (n=5)	No solution (n=3), assistance (n=1), using tablet splitter (n=1)
No equal halves/crumbles (n=4)	Take another (n=2), administration of pieces (n=1), using tablet splitter (n=1)
Measuring correct volume (n=1)	No solution (n=1)

Practical problem	Management strategy
Dissolution/disintegration of medicine (n=6)	No solution (n=6)
Drug taking (n=28, by 17 participants)	
Medicine sticks in throat/mouth (n=17)	Taking additional water or food (n=12), Breaking tablet (n=2), No solution (n=2), Taking the product before the other products (n=1)
Locating product in mouth (n=1)	No solution (n=1)
Unpleasant taste (n=10)	Drug taking with food or additional water (n=5), Taking the product before the other products (n=2), No solution (n=2), Swallowing complete tablet instead of chewing (n=1)

Handling immediate packaging

Thirty-eight participants reported a total of 73 problems with handling the immediate packaging (table 1). Most of these problems (n=43) concerned the removal of tablets or capsules, with tablets breaking, crumbling, or being damaged in another way when removing them from blister packing (n=14). Participants took the damaged medicine (n=9), took another dosage (n=2), or tried to avoid damaging the medicine by opening the lidding foil carefully with their nails (n=2). In three cases, the unintended breaking of a tablet was considered to potentially cause moderate discomfort or clinical deterioration (table 2). For example, one participant who used glibenclamide for the treatment of type 2 diabetes risked fluctuations in blood glucose levels by taking tablet parts instead of a whole, undamaged tablet:

"It often breaks when I'm pressing it out. You see, there is a groove in the tablet and it nearly always breaks. I always have to look to see where the other half of the tablet is. I often find it lying somewhere else. It also seems to be softer. It's just the way I press the tablets out I think.
I try to be careful when I am doing it so that it doesn't break in half, and sometimes it works and sometimes it doesn't. Then it breaks by the groove in the tablet and I consume the tablet parts as a whole, so to say. This is not a problem. However, what does happen is that the tablet disintegrates quickly. It becomes soggy quickly."
(Male, 71 years, glibenclamide 5 mg, immediate-release tablet)

IMAGE 1 Jar opener

TABLE 2 Details of the cases assigned as class 3 or class 2 relevance

Practical problem	Management strategy	Case	Potential clinical relevance
Reading and understanding instructions for use			
Worried by the side effects listed in the package insert (n=1)	Participant took the tablets every other day instead of once every day as prescribed	pantoprazole 20 mg	Class 3
Handling immediate packaging			
The tablet breaks or crumbles when the patient removes it from the blister (n=3)	Participant administered the resulting pieces and crumbles	enalapril 20 mg, furosemide 40 mg, glibenclamide 5 mg	Class 2
Preparation prior to use			
Difficulty with the identification of the medicine (n=1)	No strategy reported	pantoprazole 20 mg	Class 2
Difficulty filling measurement cup with correct volume (n=1)	No strategy reported	promethazine 1 mg/ml	Class 2
Difficulty with the identification of the different strengths (n=1)	Participant wrote indication on packaging	levodopa/benserazide 200/50 mg and 100/25 mg	Class 3
Tablet does not break into equal halves and/or crumbles (n=2)	Participant administered the unequal halves	phenprocoumon 3 mg	Class 3
Drug taking			
Lodging of tablet in mouth/throat when swallowing (n=1)	Participant swallowed the tablet with an additional amount of water	alendronic acid 70 mg	Class 2
Tablet has an unpleasant taste (n=1)	Participant swallowed the tablet with yoghurt	ferrous fumarate 200 mg	Class 3

* Potential clinical relevance; Class 2: potential to result in moderate discomfort or clinical deterioration; Class 3: potential to result in severe discomfort or clinical deterioration.

Other problems with the handling of the immediate packaging concerned difficulty with first-time opening of tamper-resistant containers (n=13) and with opening containers every time the medicine was needed (n=7), particularly for medicines in child-resistant bottles (n=5). Reported ways to cope with these problems were to ask the help of a partner or care-giver (n=7) and to use a jar opener (n=2) or a knife (n=4) (Image 1). One participant with rheumatism experienced problems with opening the immediate packaging for four of her nine prescribed oral medicines. This participant lived alone and was dependent on home care to help with the initial opening of one of the containers with a tamper-resistant closure; she used a paper knife to open the same container daily and scissors to remove other medicines from their blister packs.

Preparation prior to use

Twenty-three participants reported a total of 38 problems when preparing a medicine for administration (table 1). Difficulty identifying medicines after they had been taken from their

packaging was reported 10 times. One participant had difficulty distinguishing between two tablets of different strengths of the same medicine because of their similarity in appearance (levodopa/benserazide 100/25 mg and 200/50 mg, Image 2). This was considered to potentially cause moderate discomfort or clinical deterioration because accurate intake of this medication is important to control Parkinson's disease (table 2):

"So, if I have this <participant holds up the bottle of levodopa/benserazide>, but then it is bigger than this I believe. I find it difficult to tell. You have to be careful. When you put them next to each other it's easier to see, so then you know what you're doing. But in the beginning I thought, oh, they are lying there and it turned out that it was the other one. I should have been told this when I was given the instructions. So, at first I was taking them randomly because I couldn't see what I was doing. And only when it is pointed out to you, you realise what you're doing. And that is also the case for the 250 and 125. I had to get used to it at first but after a while it was OK."
(Male, 74 years, levodopa/benserazide 100/25 mg and 200/50 mg tablet)

IMAGE 2 **Look-alike medication (benserazide/levodopa 200/50 mg and 100/25 mg)**

Problems dividing tablets (n=9) were reported, with breaking tablets being described as difficult and/or painful (n=5) or resulting in unequal parts or crumbles (n=4) (Image 3). This was considered to potentially cause severe discomfort or clinical deterioration in one participant who was taking phenprocoumon, which is used for the prophylaxis and treatment of thromboembolic disorders, because of the narrow therapeutic index of the drug (table 2):

"A fine tablet, except, and I'll just take one out to demonstrate. I have to take half a tablet. There is a nice groove. I have good fingernails, see, that fit nicely into the groove. Nine times out of ten I break the tablet in two, and one-half is so big and the other half so big. So, I don't take the same amount each day. I think this might alter the thinning of my blood."
(Male, 73 years, phenprocoumon 3 mg tablet)

One participant who used promethazine for insomnia reported difficulties filling the provided measuring cup with the oral solution to the correct level. Because of the risk of overdosing, this was considered to potentially cause moderate discomfort or clinical deterioration (table 2).

IMAGE 3 Damaged tablet after attempt to break it into equal halves

Drug taking

Seventeen participants reported a total of 28 problems related to the actual taking of their medicines (table 1). Medicine lodging in the mouth or throat was reported 17 times. To get round this problem, tablets were taken with additional water or some food (n=12) or were divided (n=2). For one participant, who used alendronic acid for osteoporosis, the reported difficulty with swallowing was considered to potentially cause moderate discomfort or clinical deterioration due to the possible development of esophagitis or oesophageal ulceration (table 2):

"It's just that I think the tablet is too big to swallow. I drink a lot of warm water. Then it doesn't get stuck. And, you are not allowed to break the tablet, so I take it with a lot of water, warm or hot water. I prefer it like this. Just like drinking a cup of tea – not tepid, nice and warm. I also drink warm water in the summer, usually a whole glassful."
(Female, 83 years, alendronic acid 70 mg tablet)

Medicines were reported to taste unpleasant ten times. One participant reported swallowing medicines with yoghurt to mask the taste. As one of these medicines was ferrous fumarate, this was considered to potentially cause severe discomfort or clinical deterioration due to decreased absorption of iron (table 2):

"It is rather large to swallow. I start in the morning with seven and that is an awful lot. Because you sometimes have to really chew on them. I say chew because they are quite difficult to consume properly. Nowadays, I take those that don't go down so well with a little yogurt and then I put them in my mouth with a spoonful of yogurt that is a little sour and the tablet slips down. I do this with the large one, but also with the small ones, because one of them is bitter. And this is usually quite unpleasant." (Female, 83 years, ferrous fumarate 200 mg tablet)

Discussion

Main findings and comparison with other studies

The vast majority (95%) of the study participants experienced one or more practical problems with the use of their oral prescription medicines, ranging from problems with reading and understanding instructions for use, handling the outer packaging and especially the immedi-

ate packaging of the medicine, and making any preparations prior to use, in addition to actually taking the medicine. Most participants developed strategies to overcome the practical problems they experienced. Although several participants experienced the same problem, the potential clinical implications differed per participant because they used different medicines and different strategies to resolve the problem. At least one of the problems of 10 participants (17%) was considered potentially harmful – there were a total of 11 potentially clinically relevant problems. Most (95%) problems were considered not to be clinically meaningful, but even so they cause inconvenience and should be resolved. Moreover, if a person experiences problems with multiple medicines, there is a greater likelihood that these problems will adversely affect health. This is especially likely among frail patients with physical limitations trying to cope with complex medication regimens. Although this study investigated oral medications, similar problems may arise with non-oral dosage forms, such as eye drops[23, 26], sublingual sprays[27], and inhalers.[10, 23]. Another safety concern, specifically for patients with poor vision, rheumatoid arthritis, or Parkinson's disease, is the use of potentially harmful tools such as scissors or knives to open medicine packaging.

Strengths and limitations

This study evaluated the sequence of medication-handling actions that patients perform when taking oral medications. Previously unreported practical problems were identified, such as difficulties with opening the carton box; separating linked sachets, vials or blister cups; holding medicines; and dissolving powders for oral solution or suspension. The strategies participants used to manage these problems and the potential clinical consequences of these strategies were investigated. Previous studies, which were limited mostly to predetermined practical problems, did not investigate the participants' management strategies or focused on medication adherence without discussing clinical consequences.[4, 14, 16] Information about the practical problems and management strategies was reported by the participants, which could introduce reporting bias and recall bias. Unusual practical problems might have been missed. For example, a previous study demonstrated that older people frequently experience problems with the use of peel-off blisters.[28] This problem was not reported in the current study, possibly because only a limited number of medicines were packed in peel-off blisters. However, because participants were recruited from two different settings and the level of saturation was rather strict, it is unlikely that unusual practical problems were missed.

Implications for drug developers and practice

The practical problems that older people may encounter with the daily use of their medicines should be taken into consideration during the development, evaluation, prescription, and dispensing of medicines. The pharmaceutical industry can address the needs and concerns of older people during the development of medicines. Currently, the patient information leaflet appears to miss its main aim – at least for older patients – of providing relevant information about the use of the medicine by containing too much, too difficult, and too distressing information. Moreover, the design of medicine packaging needs to take the decreased hand-grip strength and manual dexterity of older people into consideration, and it will be challenging to develop tamper-resistant and child-resistant closures that can be used by older people. The usability of not only pill bottles and containers, but also blister packs could

be improved. Furthermore, the visual identification of medicines needs to be improved, to decrease the possibility that patients confuse medicines. Preferably, medicines should be available in appropriate dosage strengths, so that the need for subdivision is reduced to a minimum. Break marks should make it easy to break tablets into equal parts. The ease of holding and swallowing the medicine should be taken into consideration during formulation development, since older people have decreased fine motor skills and experience swallowing difficulties more often than younger adults.[29] The pharmaceutical industry may investigate the suitability of medicines for use by older people by user testing in this population during drug development. Regulatory agencies should consider the suitability of medicines for use by older people when evaluating new medicines. Healthcare providers should also address potential practical problems with medication use when prescribing and dispensing medicines to older people; for example, by selecting a dosage strength that does not need to be divided or a dosage form that causes fewer swallowing difficulties. Pharmacists and pharmacy technicians have a role in explaining to patients how packaging can be opened properly, suggesting helpful tools, and why medicines should be taken in a certain way and dosage.[30, 31]

Conclusions

Older patients provided information about their medicine use and the strategies to manage these problems. These problems, ranging from problems with reading and understanding instructions for use, handling the outer packaging and especially the immediate packaging of the medicine, and making any preparations prior to use, in addition to actually taking the medicine, may lead to incorrect medication use that may have clinical consequences. The resulted in a classification of the practical problems older people experience when taking their medicines. All stakeholders concerned with the development, evaluation, prescription, and dispensing of medicines to older people can and should help diminish the practical problems that people in this age group experience.

References

1. Nikolaus T, Kruse W, Bach M, Specht-Leible N, Oster P, Schlierf G. Elderly patients' problems with medication. An in-hospital and follow-up study. *Eur J Clin Pharmacol* 1996; 49(4):255-9.
2. Kelly J, D'Cruz G, Wright D. Patients with dysphagia: experiences of taking medication. *J Adv Nurs* 2010; 66(1):82-91.
3. Ruscin JM, Semla TP. Assessment of medication management skills in older outpatients. *Ann Pharmacother* 1996; 30(10):1083-8.
4. Kairuz T, Bye L, Birdsall R, Deng T, Man L, Ross A, et al. Identifying compliance issues with prescription medicines among older people: a pilot study. *Drugs Aging* 2008; 25(2):153-62.
5. Stegemann S, Ecker F, Maio M, Kraahs P, Wohlfart R, Breitkreutz J, et al. Geriatric drug therapy: neglecting the inevitable majority. *Ageing Res Rev* 2010; 9(4):384-98.
6. Isaac LM, Tamblyn RM. Compliance and cognitive function: a methodological approach to measuring unintentional errors in medication compliance in the elderly. McGill-Calgary Drug Research Team. *Gerontologist* 1993; 33(6):772-81.
7. Ostrom JR, Hammarlund ER, Christensen DB, Plein JB, Kethley AJ. Medication usage in an elderly population. *Med Care* 1985; 23(2):157-64.
8. Tordoff JM, Bagge ML, Gray AR, Campbell AJ, Norris PT. Medicine-taking practices in community-dwelling people aged > or =75 years in New Zealand. *Age Ageing* 2010; 39(5):574-80.
9. Atkin PA, Finnegan TP, Ogle SJ, Shenfield GM. Functional ability of patients to manage medication packaging: a survey of geriatric inpatients. *Age Ageing* 1994; 23(2):113-6.
10. Thwaites JH. Practical aspects of drug treatment in elderly patients with mobility problems. *Drugs Aging* 1999; 14(2):105-14.
11. Barends DM, Groot DW, van der Steen JC, de Kaste D, Frijlink HW. Results of a market surveillance study in The Netherlands on break-mark tablets. *Pharmeur Sci Notes* 2006; 2:1-7.
12. Windham BG, Griswold ME, Fried LP, Rubin GS, Xue QL, Carlson MC. Impaired vision and the ability to take medications. *J Am Geriatr Soc* 2005; 53(7):1179-90.
13. Griffiths R, Johnson M, Piper M, Langdon R. A nursing intervention for the quality use of medicines by elderly community clients. *Int J Nurs Pract* 2004; 10(4):166-76.
14. Schiele JT, Quinzler R, Klimm HD, Pruszydlo MG, Haefeli WE. Difficulties swallowing solid oral dosage forms in a general practice population: prevalence, causes, and relationship to dosage forms. *Eur J Clin Pharmacol* 2013; 69(4):937-48.
15. Denneboom W, Dautzenberg MG, Grol R, De Smet PA. User-related pharmaceutical care problems and factors affecting them: the importance of clinical relevance. *J Clin Pharm Ther* 2005; 30(3):215-23.
16. Orwig D, Brandt N, Gruber-Baldini AL. Medication management assessment for older adults in the community. *Gerontologist* 2006; 46(5):661-8.
17. Van Geffen K, Meuwese E, Philbert D, Bouvy M. [Problems with medicine packages. Experiences reported to a Dutch medicine reporting system]. *Pharm Weekbl* 2009; 3(11):199-203.
18. Cameron KA, Richardson AW. A guide to medication and aging. *Generations* 2001; 24(4):8-21.
19. Hughes RG. Patient Safety and Quality: An Evidence-Based Handbook for Nurses. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
20. Logue RM. Self-medication and the elderly: how technology can help. *Am J Nurs* 2002; 102(7):51-5.
21. Overgaard AB, Hojsted J, Hansen R, Moller-Sonnergaard J, Christrup LL. Patients' evaluation of shape, size and colour of solid dosage forms. *Pharm World Sci* 2001; 23(5):185-8.

22. van der Steen KC, Frijlink HW, Schipper CM, Barends DM. Prediction of the ease of subdivision of scored tablets from their physical parameters. *AAPS PharmSciTech* 2010; 11(1):126-32.

23. Blenkiron P. The elderly and their medication: understanding and compliance in a family practice. *Postgrad Med J* 1996; 72(853):671-6.

24. Ward J, Buckle P, John Clarkson P. Designing packaging to support the safe use of medicines at home. *Appl Ergon* 2010; 41(5):682-94.

25. Cornish PL, Knowles SR, Marchesano R, Tam V, Shadowitz S, Juurlink DN, et al. Unintended medication discrepancies at the time of hospital admission. *Arch Intern Med* 2005; 165(4):424-9.

26. Dietlein TS, Jordan JF, Luke C, Schild A, Dinslage S, Krieglstein GK. Self-application of single-use eyedrop containers in an elderly population: comparisons with standard eyedrop bottle and with younger patients. *Acta Ophthalmol* 2008; 86(8):856-9.

27. Tordoff J, Simonsen K, Thomson WM, Norris PT. "It's just routine." A qualitative study of medicine-taking amongst older people in New Zealand. *Pharm World Sci* 2010; 32(2):154-61.

28. Philbert D, Notenboom K, Bouvy ML, van Geffen EC. Problems experienced by older people when opening medicine packaging. *Int J Pharm Pract* 2014; 30(1):3-7.

29. Stegemann S. Challenges and opportunities in the design of age-appropriate drug products. *Z Gerontol Geriatr* 2012; 45(6):479-84.

30. Vinks TH, de Koning FH, de Lange TM, Egberts TC. Identification of potential drug-related problems in the elderly: the role of the community pharmacist. *Pharm World Sci* 2006; 28(1):33-8.

31. Vinks TH, Egberts TC, de Lange TM, de Koning FH. Pharmacist-based medication review reduces potential drug-related problems in the elderly: the SMOG controlled trial. *Drugs Aging* 2009; 26(2):123-33.

Supplementary information

Summary of topic list

A. Demographic information on participants

1. Gender
2. Date of birth
3. Living situation (alone, together with partner or relatives)
4. Social situation (children, no children)
5. Highest level of education
6. Any help with the use of medicines (partner, home-care)

B. Questions for each medicine

General information

1. Purpose of use of medicine (according to participant)?
2. How to use medicine (according to participant? Route of administration, regimen
3. When is medicine actually administered?
4. How do you know how to use this medicine?
5. Where do you store this medicine?

Information on packaging and labelling

1. Reading information on the packaging and pharmacy labelling? Why/why not?
2. Experience with the information on the packaging and pharmacy labelling
   - Size of text, readable? Information understandable? Easy to remember? Any tricks or help?
3. Use according to the instructions on the pharmacy labelling? Why/why not?

Patient information leaflet

1. Reading patient information leaflet? Why/why not?
2. Experience with patient information leaflet?
   - Size of text, readable? Information understandable? Easy to remember? Any tricks or help?
3. Use according to the instructions of the patient information leaflet? Why/why not?

Packaging

Outer packaging

1. Medication packed in its original outer packaging? Why not?
2. Identification of packaging, distinguishable from other medicines?
3. Experience with the packaging? Size?
4. Able to open/close the packaging? Why/why not? Any tricks or help?

Immediate packaging

1. Medication packed in its original immediate package? Why not?
2. Identification of packaging, distinguishable from other medicines?

3. Experience with packaging, easy to use? Why/why not? Any tricks or help?
4. Able to remove the product from the packaging? Why/why not? Any tricks or help?
5. Does medicine remain intact after removal from packaging? Why/why not? Any tricks or help?

Formulation and presentation

1. Experience with route of administration. Able to administer medicine?
2. Able to identify the medicine, distinguish it from other medicines?
3. Able to hold the medicine? Why/why not? Tricks/help?
4. Able to swallow the medicine? Why/why not? Tricks/help?
5. Any need to split the tablet? Experience therewith? Any tricks, tools or help needed?

Medical aids (if applicable)

1. Is a medical aid required to use this medicine, e.g. measuring cup or spoon?
2. Experience with use of device?
3. Able to use this device? Why/why not? Tricks/help?

Coding scheme

A. Codes for practical problems with medication use

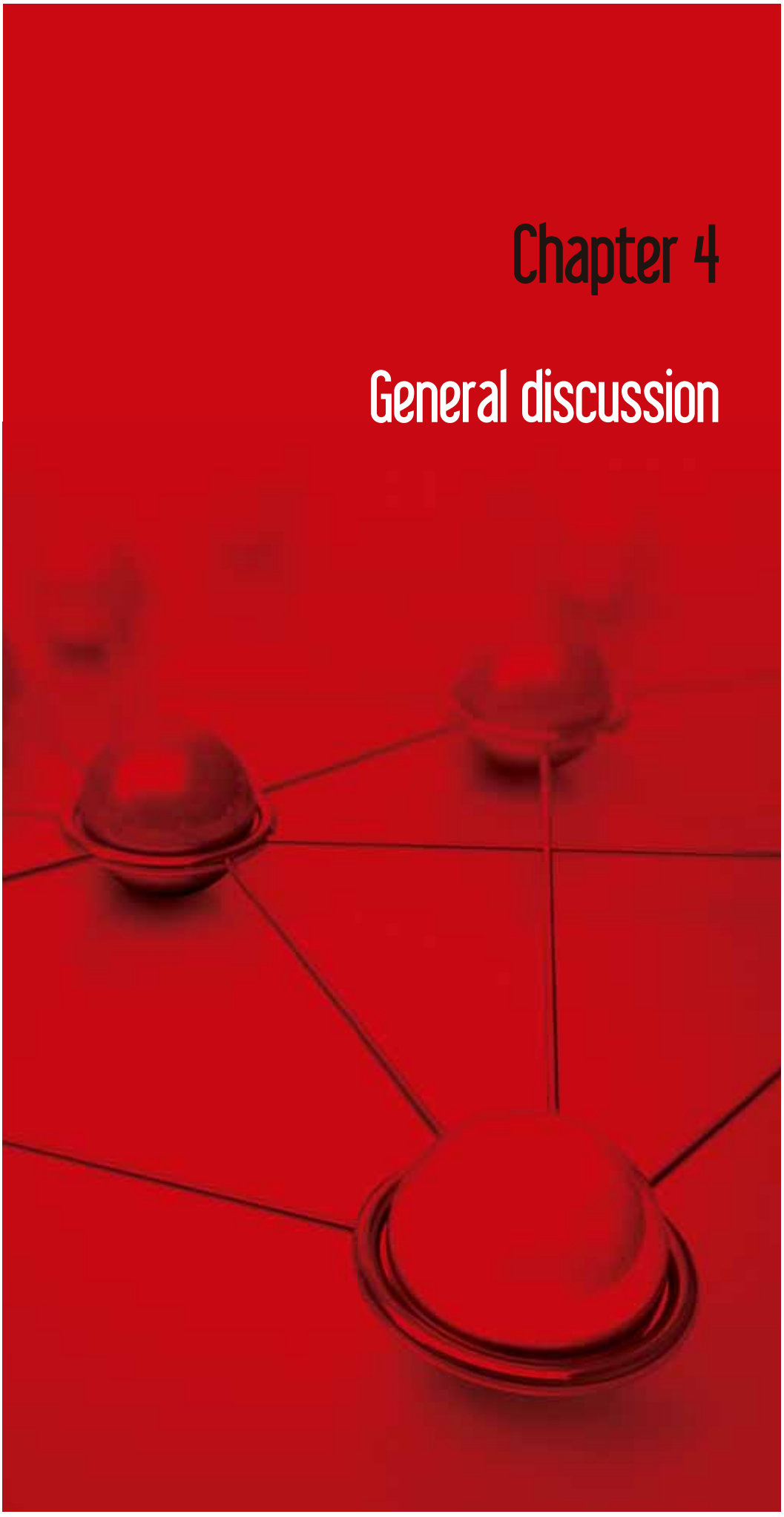
- **Instructions for use**
  - Packaging
    - Text too small to read
  - Pharmacy labeling
    - Text too small to read
    - Information too difficult to understand
    - Too much information
  - Patient information leaflet
    - Text too small to read
    - Information too difficult to understand
    - Too much information
    - Worried by information about side effects
- **Accessing medication**
  - Outer packaging
    - Identification of packaging
    - Opening carton bo
      - Perforation line for opening invisible
    - Removing blister from carton box
    - Opening aluminium pouch covering blister
    - Separating sachets from each other
      - Tearing of adjacent sachet, resulting in leaking
    - Separating pockets of a blister strip
      - Tearline doesn't tear
    - Separating single use vial from strip
      - More than one vials opens
  - Immediate packaging
    - Opening bottle/container for first time
    - Opening bottle/container every time
    - Removing medicine from bottle/container
    - Removing medicine from blister
      - Pockets are too small to push on
      - Difficult to localise medicine
        - Pockets are too large
      - Tearline tears instead of opening foil
        - Pockets are too large
      - Pockets are too close to each other to push only one
      - Capsule opens
      - Capsule dents
      - Time-consuming
    - Medicine breaks or crumbles
    - Closing botte/container
      - Medicine breaks or crumbles
- **Preparation for use**
  - Identification of medicine
  - Difficult to hold medicine
  - Tablet breaking is difficult or painful
  - Tablet does not break in equal halves
  - Tablet crumbles when breaking
  - Unable to fill correct volume in measuring device
  - Medicine does not dissolve or disintegrate completely
- **Actual drug taking**
  - Swallowing
    - Medicine sticks in mouth/throat
    - Not able to feel/locate medicine in mouth
    - Medicine has an unpleasant taste
  - Chewing
    - Medicine has an unpleasant taste

B. Codes for management strategies

- **Change to packaging**
  - Removing stopper from cap
  - Using other primary packaging
- **Assistance**
  - Nurse/care giver
  - Partner
- **Tool**
  - Auxiliary aid
    - Tablet splitter
    - Jar opener
    - Magnifying glass
  - Other equipment
    - Knife
    - Paper knife
    - Spoon
    - Scissors
      - To separate pockets
- **Trick**
  - Drug taking with food (non-dairy)
  - Drug taking with dairy
  - Dissolution of medicine in (hot)beverage
  - Taking this medicine before others
  - Use wet finger tip
  - Remove 2 tablets at once
  - Add extra water to residue
  - Opening carton box different way
  - Use extra light
  - Push and twist with palm of hand
  - Using nails to open lidding foil
  - Using nails to sharpen tearline
  - Not closing immediate packaging properly
  - Rupture carton box
  - Swallow with additional amount of water
- **Dosage form modification**
  - Breaking tablet in pieces
  - Swallow undissolved tablet with water
  - Swallowing without chewing
  - Dissolution/disintegration in water
- **Different dosage or frequency**
  - Using no or lower dose
- **Other solution**
  - Try again/time consuming
  - Writing on packaging
  - Take another dosage
  - Administration of pieces
  - Pick up and administer
  - Read information on packaging
  - Store separate from look-a-like medicine
  - Reading embossment on tablet
  - Leave patient information leaflet away
  - Not reading patient information leaflet
- **No solution**

Chapter 4

General discussion



Introduction

Compared with younger adults, people aged 65 years or older are in general more likely to experience negative effects of medication. This risk becomes even more pronounced among people older than 75 years, due to their use of multiple medicines, comorbidities, frailty, physical and cognitive impairments, and prescribing errors or communication errors between healthcare professionals.[1, 2] Relatively little is known about the effectiveness and safety of drugs in older people, especially in frail individuals, because they tend not to be included in clinical trials.[3-20] As rational drug prescribing to older patients depends on information about the effectiveness and especially the safety of medicines in the older population, the principal objective of the studies reported in this thesis was to investigate the availability of information to help healthcare professionals to prescribe rationally to older people. We evaluated the availability and clinical applicability of information for healthcare professionals, and analysed the evidence base of information originating from clinical practice.

We found that while the proportion of older people in pre-approval trials of medicines for diseases characteristically associated with ageing was appropriate for certain medicines, the use of age-sensitive exclusion criteria restricted the representativeness of trial populations. In addition, the proportion of older people in clinical trials of medicines for diseases not uniquely associated with old age was much lower than the proportion of older people affected by these diseases in daily practice (Chapter 2.1). In addition to the shortcomings of some pre-approval trials, there were also discrepancies between the findings of post-approval randomised safety outcomes trials and those of studies in a daily practice setting (Chapter 3.1). Previously undetected adverse drug reactions (ADRs) may become apparent during the post-approval phase. We reported an example of the value of spontaneous reporting, namely, the detection of hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in four older patients using valproic acid (Chapter 3.2).[21] Older people also experience practical problems when using medicines (Chapter 3.3). In several cases, the strategies used to cope with these problems could adversely affect the patient's clinical condition.

In addition to investigating the evidence base of information for rational prescribing to older people, we also investigated the availability of drug information about older people in the summaries of product characteristics (SmPCs) (Chapter 2.2).[22] The SmPCs contained about half of the items considered relevant to rational prescribing, whereas the information was fairly well represented in the European public assessment reports. In national European and US drug compendia, which are based on the SmPC, information to support rational prescribing to older people was poorly available or not applicable (Chapter 2.3). Moreover, drug developers and regulators did not appear to share entirely healthcare professionals' views about the necessity of making drug information about older people collected during the pre-approval phase available for use in daily practice (Chapter 2.4).[23]

In this chapter, the studies presented in this thesis are discussed in broader perspective. We address the evidence, availability and applicability of information to support rational prescribing to older people, including implications and suggestions based on the findings in this thesis.

The rational prescribing of drugs to older people is dependent on evidence about the effectiveness and safety of medication in the older population. This information needs to be available to healthcare professionals and applicable in daily practice.

Evidence base of information for rational prescribing to older people

The collection of information about the effectiveness and safety of medicines in older people starts before a medicine is approved for the market and continues throughout the post-marketing phase. The International Conference on Harmonization (ICH) guideline on geriatrics (E7) describes what investigations should be carried out in older people in the pre-approval phase, and what information should be described in the application dossier of a new medicinal product in order to receive market approval.[24] In addition, before marketing approval is given, applicants have to prepare risk management plans that describe investigations planned after authorisation.

The ICH E7 guideline states that participants aged 65 years or older with concomitant illnesses or comedication must be included in clinical trials.[24] This means that the number, proportion, and characteristics of the patients included should reflect those seen in real life.[24-26] In addition, the guideline specifies that in trials of medicines for diseases characteristically associated with old age, such as Alzheimer's disease, atrial fibrillation, and osteoporosis, at least 50% of the participants should be aged 65 years or older. Trials of medicines for diseases present in, but not unique to, older people, such as type 2 diabetes mellitus, depression, and convulsions, should include at least 100 participants aged 65 years or older. In 2010, the European Medicines Agency (EMA) published the questions and answers (Q&A) document as supplement to the ICH E7 guideline.[26] In recognition of the increasing number of older patients, the recommendation about the minimum number of older participants in clinical trials was adapted to include the entire spectrum of the geriatric population, with usually more than 100 older participants being considered appropriate.

In the studies described in this thesis, we investigated the participation of older people in pre-approval clinical trials of medicines that eventually received marketing approval between 2008 and 2011. These medicines were either for diseases characteristically associated with ageing or for diseases not uniquely present in old age (Chapter 2.1). In this way, we evaluated adherence to the ICH E7 guideline. The proportion of older participants in trials of medicines for diseases typically associated with ageing was encouraging, with more than half of the study population consisting of individuals aged 65 years or older, and almost 20% consisting of individuals aged 75 years or older. Hence, the recommendations regarding the proportion of older subjects as described in the ICH E7 guideline were met. However, many studies used exclusion criteria that indirectly affected the inclusion of older people. For example, the use of concomitant medication, comorbidities, inability to give informed consent, and communication barriers negatively affected the representativeness of the study population. While trials of three of five medicines for diseases not uniquely present in old age included more than 100 participants aged 65 years or older, as recommended in the ICH E7 guideline, the proportion of older people included in all these clinical trials was much lower than the proportion

of older people affected by these diseases in daily practice. Moreover, subjects older than 75 years comprised only 1% of the study population. For example, 20% of the trial population in type 2 diabetes trials consisted of patients aged 65 years or older and 2% of people aged 75 years or older. This is surprising, given that most people with diabetes in developed countries are older than 65 years and 15% are older than 80 years.[27] We found that the participation of members of the target population was limited, which could affect the generalizability of the efficacy and safety findings of these pre-approval trials.

Medication safety was also found to differ in post-approval randomised safety trials and in daily practice (Chapter 3.1). We evaluated the absolute risk of upper gastrointestinal (GI) events during the use of non-selective NSAIDs (nsNSAIDs) and cyclooxygenase-2-inhibitors (coxibs) in patients aged 65–74 years and older than 75 years in daily practice and compared the magnitude of this risk with that reported in randomised clinical trials (RCTs). The risk of upper GI events was higher in patients aged 75 years and older than in patients aged 65–74 years in daily practice. The risk of upper GI events in older patients in general practice was lower than that suggested by the findings of RCTs. However, the rates of GI events reported in RCTs varied greatly and our research findings may have been affected by differences in baseline risk in the study populations and in the way GI events were quantified. Despite these possible limitations, the study underlined the importance of observational studies in daily practice to complement what has been learned from RCTs.

The limited representativeness of clinical trial results affects the evidence base on the safety and effectiveness of medication.[28] Spontaneous reporting of suspected adverse effects is a valuable way to fill this knowledge gap in the post-marketing phase.[29] It generates knowledge of harmful drug effects at the individual level and at the population level.[30] If applied in daily practice, this knowledge facilitates the safer use of medication. In Chapter 3.2, we described four spontaneous reports of hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) as a suspected adverse drug reaction (ADR) to valproic acid, an anticonvulsive agent.[21] Hyponatraemia and SIADH are more common in older people than in younger adults.[31] These conditions are, even when mild, associated with increased morbidity and mortality.[32, 33] Causality was probable in the cases. An analysis of safety data in the post-marketing pharmacovigilance Vigibase confirmed the association.

Safety and efficacy are not the only aspects evaluated before marketing approval is given – practical aspects of medicine use and the suitability of packaging are also investigated. However, in many cases, these aspects are investigated in studies including relatively healthy, younger adults,[34] so that the generalizability of findings to older adults is compromised. Older people experience a number of practical problems when using medication, such as difficulty opening packaging.[35-43] If they cannot open the packaging, they do not use the medicine, which leads to poor medication adherence.[37, 44] In turn, suboptimal adherence may decrease the effectiveness of a medicine or increase its risks. The risks appeared to be increased in the qualitative study presented in Chapter 3.3. The vast majority (95%) of the 59 study participants aged 70 years and older experienced one or more practical problems when trying to take their oral prescription medicines. These problems ranged from difficulties reading and understanding instructions for use, handling the outer packaging and especially

the immediate packaging of the medicine, and making preparations prior to use, in addition to actually taking the medicine. Most individuals found strategies to manage these problems, but in 11 cases the problems and solutions could potentially lead to clinical deterioration of the patient's condition.

Implications

The restricted generalizability of the results of pre-approval and post-approval clinical trials influences the benefit/risk assessment of medicines for older individuals in real life. The evidence base can be improved, but this can only be achieved if all parties involved join forces. Stakeholders that play a role include pharmaceutical companies and regulatory agencies; contract research organisations; suppliers of services, systems and equipment; academics, investigators, research ethics committees; patient organisations; and, last but not least, older people and their carers or legal representatives.

Drug developers and regulators

Two vital stakeholders in improving the representativeness of older people in clinical trials are pharmaceutical companies and regulatory agencies. The adoption of the ICH E7 guideline in 1994 was a first official step, followed by several efforts to improve the evidence base of information about older people. In 2006, the EMA's committee for medicinal products for human use (CHMP) drew the conclusion that adherence to the ICH E7 guideline was adequate.[45] The ICH E7 Q&A guideline, published in 2010, explains the items mentioned in the ICH E7 guideline and describes adaptations made necessary by population ageing. In 2011, the EMA published its geriatric medicines strategy, in which it states that the needs of the older population should be taken into account in pre-approval and post-approval studies. The EMA also established the geriatric expert group (GEG), which consists of clinical experts. This group provides scientific advice on specific aspects of the development of medicines used by older patients and on the assessment of products or pharmacovigilance issues.[46] The GEG is a step in the direction of collaboration between stakeholders, provided that its members have the opportunity to integrate the needs of older patients and healthcare professionals in guidelines and assessments of new medicines.

In October 2013, pharmaceutical companies, represented in the European Federation of Pharmaceutical Industries and Associations (EFPIA), published a position paper on how they can improve the evidence base of drug information about older people.[47] In addition, the European Forum on Good Clinical Practice (EFGCP) has recently published an ethical guideline on good clinical practice in investigations involving older people.[48] The EFGCP is an example of diverse stakeholders joining forces, as it is a not-for-profit organisation of individuals involved in biomedical research, such as pharmaceutical companies, regulatory agencies, academia, and patient organisations.[49]

On the basis of the ICH E7 guideline, the ICH E7 Q&A recommendations, the EFPIA position paper, the EFGCP guidance, and the findings of the studies reported in this thesis, the following recommendations can be made for improving the evidence base of drug information for rational prescribing to older people.

First, it is important that the target population is appropriately reflected in clinical trials. Rather than minimally 100 participants aged 65 years and older, the number and proportion of older study participants should reflect the number of individuals affected by the disorder for which the medicine is prescribed in daily practice. Every effort should be made to enrol older participants, although it is recognised that this can be challenging.[26] Informed consent should be sought in all older people that are able to consent. If older subjects do not fully understand the nature, purpose, and implications of participation in a clinical trial, their assent could be sought, in combination with the assent or consent of their authorised representative.[48] With this procedure, more vulnerable older people will be eligible for participation in clinical trials.

Second, with respect to exclusion criteria, all parties emphasize that upper age cut-offs are no longer permissible.[24, 26, 47, 48] The use of concomitant medication and the existence of multiple comorbidities should be allowed as much as possible. For example, patients with diabetes mellitus and a decreased renal function who use ACE inhibitors, antihypertensive agents, and statins should be allowed to participate in clinical trials of glucose-lowering medicines. Since multimorbidity is the norm in older people, exclusion criteria should be fully justified and not disproportionally affect older people. Previous studies of the justification of exclusion criteria could serve as a basis for this.[9, 50] However, in our opinion, two exclusion criteria that were regarded as fully justified in these studies should be reconsidered. First, any comorbid illness that limits life expectancy was considered a fully justifiable exclusion criterion.[9] While, of course, it is preferable that a patient completes follow-up, we would suggest that this exclusion criterion be specified with respect to the duration of follow-up, by excluding only those patients who will probably die during the follow-up period due to concomitant disease. Second, the inability to attend follow-up evaluations was considered fully justifiable. Yet, if older people representative of the target population are to be included in clinical trials, then follow-up evaluations should be offered, where possible, at the individual's home or in their general practitioner's office.

Third, the efficacy, dose response, and adverse effects of medicines should be evaluated for age-related differences. The ICH E7 Q&A guideline specifically recommends investigating effects on cognitive function, balance and falls, weight loss, sarcopenia, urinary incontinence and retention, and drug–disease interactions. On the basis of our findings, we would suggest this list be extended to include locomotor (anti-dopaminergic) effects, sedative (anti-α-adrenergic) effects, negative effects on cardiovascular function, and effects on homeostasis.[23] In this way, information considered necessary for healthcare professionals in daily practice would be available at time of market approval of a new medicine.

Fourth, the ICH E7 Q&A guideline proposes older participants be classified into three age subgroups, 65–74, 75–84, and 85 years and older.[26] This seems unnecessary because chronological age does not reflect biological age. Moreover, differences in health status will have a relatively larger confounding effect if the age strata are smaller.

Fifth, an as yet unaddressed issue in the current statements and position papers is the practical usability of medication and its packaging. Since older people experience practical problems

when using their medication, we think that the practical use of the medicine and its packaging should be investigated in older trial participants.

Lastly, the ICH E7 Q&A guideline states that it could be appropriate to collect data post-marketing, e.g., if too few older people were recruited to a clinical trial despite the best efforts of investigators.[26] The post-marketing phase is also important for investigating the effects of medications in very frail older patients, because it is unethical to include them before the safety of a medicine has been assessed in less frail individuals.[51] In addition, because pre-approval clinical trials primarily focus on demonstrating the efficacy of a medicine, and study populations are relatively healthy and homogeneous, not all risks are known at the time of market approval. The post-marketing phase offers the opportunity to gather more information about a medicine, especially about its safety. An advantage of post-marketing studies is that actual users, many of whom have multiple morbidities and use several medications, can be investigated in daily practice. The EMA introduced post-authorisation safety studies (PASS) to improve the active identification, quantification, and confirmation of safety issues after market approval.[52] Whereas there is a delay in the reporting of potential ADRs with spontaneous reporting, investigating medicines prospectively should lead to earlier identification of ADRs. This is important, especially for frail older people.

As shown in Chapter 3 of this thesis, evidence originating from daily practice offers valuable knowledge that complements the findings of studies performed in the pre-authorisation phase. With respect to older people, information about safety measures, but also about the practical use of medicines appears important.

Since the adoption of the ICH E7 guideline, drug developers and regulators have taken steps to improve the participation of older people in clinical trials. However, our and other findings indicate that the representation of older people in trails leaves room for improvement.[3, 5, 7-9, 15, 16, 18-20] It could be argued that a guideline without legislative power is not powerful enough to convince drug developers of the importance of improving the situation. However, there is broad reluctance to introduce legal regulations. One reason for this reluctance is the experience gained with the development of drugs for another group of vulnerable patients: children. Like older people, children, from neonates to teenagers, form a heterogeneous population that has different biological and pharmacological characteristics from those of adults. To improve knowledge about the safety and efficacy of medicines in children, the European Union implemented the Paediatric Regulation.[53] One key objective of the Regulation is to obtain market approval specifically for children for the majority of medicines used by children. To achieve this goal, companies are obliged to examine every new medicinal product in development for adults for its potential for use in children, and to establish a paediatric investigation plan.[54] For a new application, compliance with the obligations is rewarded with a 6-month extension of the Supplementary Protection Certificate, which is in turn an extension of the legal patent. This is a manner to balance the extra burden and costs that drug developers have to make.[54]

Five years after the implementation of the Paediatric Regulation, the number of paediatric trials has not yet increased, but the overall number of paediatric study participants in clinical trials has.[54] The Regulation has received its share of criticism. For example, the burden on the

pharmaceutical industry is substantial, considering the duration, complexity, and economic aspects of drug development programmes.[54-56] Additionally, almost all paediatric investigation plans have to be modified one or more times. Especially the level of detail required by the paediatric committee has been criticised as being administratively rather than scientifically based.[54, 56] Furthermore, the patent extension is only of economic value for high-selling products, which constitute a minority of the medicines used by children.[54]

With respect to the older population, it is arguable that a Geriatric Regulation would be the answer. While it might seem advantageous to oblige pharmaceutical companies to include more older people and to prepare a 'geriatric investigation plan' for all medicines in development, the burden on the pharmaceutical industry would increase further, and double if a medication is to be licensed for use in both children and older individuals. Furthermore, it is possible that extra burden would be purely administrative, as with the Paediatric Regulation. Nevertheless, regulatory agencies and pharmaceutical companies need to carefully consider the burden older people experience if medicines are not appropriately investigated. Even though children and older people both belong to vulnerable populations currently underrepresented in clinical trials, the vital difference is the number that use one or more medicines – whereas children constitute an almost negligible proportion of medication users, older patients use the most medications per unit of population.[57]

Researchers and healthcare professionals

Investigators are often reluctant to include participants that have multiple morbidities and use several medicines because of potential confounding.[58] In addition, older people often depend on the help of carers for transport or for adherence to the study regimen, and this dependence is considered to be a complicating, time-consuming, and expensive factor. Healthcare professionals are typically involved in recruiting patients to trials – they tell older patients about clinical trials, assess whether they are eligible, and invite them to participate. In many cases, healthcare professionals consider that older patients should not be included in trials for the patients' own good, because they vulnerable as a result of their age or because they have multiple comorbid conditions or use polypharmacy.[58]

PREDICT, a consortium of key European geriatricians, has written a charter that includes suggestions on how to improve the recruitment of older people to clinical trials.[59] The charter describes the potential roles of several stakeholders. Considerations for healthcare professionals and researchers include stopping the under-recruiting of potentially eligible older individuals.[28, 60] The need for solid evidence in older people should prompt their inclusion in trails and generate objective and comprehensible information to enable eligible individuals to make an informed decision about their participation. Furthermore, researchers should ensure that trial participation is made as convenient as possible. Older people may need additional time or assistance. For this reason, researchers should be trained on how to carry out clinical trials involving people with decreased communication, sensory, mobility or cognitive skills.[59]

Research ethics committees

Research ethics committees could improve the representation of older people in clinical trials as well, by critically considering the risks and benefits of research in older people.[48, 59] Many

clinical trial protocols currently submitted to university or hospital ethics committees for approval use an upper age limit as exclusion criterion.[61] Exclusion criteria should be critically reviewed for unjustified exclusion based on age, comorbidity, polypharmacy, or disability, as described above.[59] Research ethics committees may benefit from the inclusion of clinicians or investigators with geriatric expertise. Communication between research ethics committees, healthcare professionals, and researchers could diminish reluctance to include a more vulnerable, but more representative, population in clinical trials.

Medical journal editors

Medical journal editors could include in their instructions to authors the requirement that exclusion criteria in clinical trials should be justified. Insight into the exclusion criteria applied in clinical trials, accompanied by a justification of their use, could make authors more critical of their study design and exclusion criteria.

Patients and their legal representatives

Patients may have erroneous ideas about the risks of unapproved medication and the advantages of medical trials to healthcare professionals, researchers, or pharmaceutical companies.[62] In addition, patients may be worried about the consequences for their treatment if they do not participate in a trial. Family members, carers, or legal representatives may have the same prejudices or consider their older relative too vulnerable to participate in a clinical trial.

Patients and their carers or legal representatives need to be aware of the possibility to participate in clinical trials. Objective information, provided by healthcare professionals and researchers, can eliminate erroneous ideas and beliefs. Two examples of initiatives to improve this awareness are AGE Platform Europe and the Clinical Research Network´s website for patients and carers, which is part of the National Institute for Health Research (NIHR) in the UK.[63, 64] Patients can also play a role in improving research, e.g., by participating in consumer organisations, such as AGE platform Europe, or EFGCP.

Availability and applicability of information

In addition to the need for a solid evidence base of information to support rational drug prescribing to older people, this information should be readily available to healthcare professionals in daily practice in a way that they can apply it to older patients. The ICH E7 guideline recommends what information should be described in the application dossier of a new medicinal product in order to receive market approval. The application dossier is not publicly available, but the regulatory considerations relevant to drug approval are publicly available in the European public assessment report (EPAR), which contains parts of the pre-authorisation dossier.[46] As a regulatory document, the EPAR is not intended for daily use. The official sources of information for healthcare professionals for the safe and effective prescribing of medicines are the summary of product characteristics (SmPC) in Europe, and the product label (PL) in the USA. It is important that drug information described in the application dossier and EPAR is adequately reflected in the SmPCs and PLs. This is particularly so

because national drug compendia are based on the SmPCs and PLs, and healthcare professionals often refer to drug compendia when choosing medicines for their older patients.[65-69]

In Chapter 2.2, we presented our investigation of the inclusion of information relevant to rational prescribing to older people in SmPCs and EPARs.[22] Nineteen recommendations mentioned in the ICH E7 guideline were investigated for their availability in the SmPCs and EPARs of 53 medicines for diseases frequently present in older people. Overall, half of the items described in the ICH E7 were available in the SmPCs and 80% were present in the EPARs. Most information about the characteristics of the study population was not available in the SmPCs, whereas about 50% of this information was present in the EPAR. As a result, healthcare professionals cannot find all the information about older people that is potentially available when they refer to the SmPC. In addition, it remains unclear whether drug information that is available in the SmPC applies to frail older patients.

In addition to the SmPCs, we investigated the availability and clinical applicability of information to support rational prescribing to older patients included in national drug compendia (Chapter 2.3). The US Physician's Desk Reference (PDR), and four European drug compendia, namely the Belgian Repertorium, German Rote Liste, British National Formulary, and the Dutch Farmacotherapeutisch Kompas, were included. The PDR contains a short summary (concise monograph) and the product label (PL), the US equivalent of the SmPC. As in the study of the SmPCs, we investigated whether the 19 items described in the ICH E7 guideline were available. In addition, we assessed the applicability of the information to daily practice. For example, "caution is warranted in older patients" was considered not being applicable, whereas "the maximum dose in patient aged 75 years or older is 50 mg" was. Overall, 19% of information about characteristics of the older population, clinical experience with older people, pharmacokinetic aspects, and drug–drug interactions was available and applicable. The Belgian Repertorium provided the least information (7%), the US PDR the most (47%). Information about the nature of the studied population was provided the least frequently (14%) and information about drug–drug interactions the most frequently (49%). Most available information was applicable, except for information about age-related differences in adverse effects and the need for monitoring renal impairment. This is worrying, because older patients frequently experience adverse effects and often have renal impairment. In conclusion, the majority of information relevant to prescribing to older people was not available in the investigated compendia, although the PDR stood head and shoulders above the other compendia as it includes the PL in an easily accessible way.

In addition to the availability and applicability of information about older people, the type of information available to support rational drug prescribing to older people in daily practice can be improved. In Chapter 2.4, we presented a study involving 43 European drug developers, regulators, and healthcare professionals with an interest in medication for older individuals.[23] They considered to what extent in daily practice healthcare professionals need information about the representation of older patients in trials and the pharmacokinetics, efficacy, safety, and convenience of use of medicines in older individuals. Most participants considered it necessary to have information about age-related differences in adverse events, particularly locomotor effects and drug–disease interactions, dosing instructions for older people, and the pro-

portion of individuals aged 65 years and older included in clinical trials. Clinicians considered information about the inclusion in clinical trials of participants aged 75 years or older, time to benefit in older people, anticholinergic effects, drug–disease interactions, and convenience of use to be significantly more important than did non-clinical respondents. In the ICH E7 guideline or its supplement, the ICH E7 Q&A, the effects of medicines on the locomotor system, drug–disease interactions, and dosing instructions are currently not addressed.

Implications

The findings presented in this thesis demonstrate that the availability and applicability of information relevant to rational drug prescribing to older people in SmPCs, PLs, and drug compendia could be improved. In addition, information considered necessary by healthcare professionals is currently not collected in pre-approval studies. For rational drug prescribing to older patients, the drug information gathered during the pre-approval and post-approval phases needs to be relevant for and applicable to older patients in daily practice. Moreover, this information should be adequately reflected in SmPCs, PLs, and drug compendia.

The drug compendia investigated in this thesis make use of information obtained from sources other than the SmPC and PL.[65, 66, 70, 71] Apparently, the need for specific guidance on rational drug prescribing in daily practice is recognised. At an international level, the NICE guidelines of the UK National Institute for Health and Care Excellence provide information for daily practice. In the Netherlands, the Expertise Centre Pharmacotherapy in Old Persons (EPHOR) provides age-specific recommendations for the use of medication by frail older patients, based on evidence of efficacy and safety in older people reported in the literature. Although the NICE guidelines and the EPHOR recommendations are valuable, the SmPCs, PLs, and drug compendia could improve the availability of relevant information about older people. On the basis of findings reported in this thesis, we suggest that the following topics be included in SmPCs, and PLs, and preferably in drug compendia (table 1).[23]

First, healthcare professionals need to know about the evidence base of the information provided – it is important to know about the characteristics of the older study population, and especially about the number of participants aged 75 years or older. In addition, exclusion criteria should be mentioned, especially those based on age, cognitive impairment, physical disability, decreased life expectancy, communication or language barriers, diminished renal function and hepatic function, past medical conditions, and concomitant medication frequently used by the older population.

Second, information about the effectiveness of the drug in older individuals is needed, as well as information about age-related differences in efficacy and in dose response. With regard to medicines for chronic conditions, it is valuable to know the time to benefit in older individuals.[72-75]

Third, safety information about older individuals is vital, since they are at greater risk of experiencing adverse effects. Older people are particularly susceptible to, e.g., sedative effects, orthostatic hypotension, cognitive deterioration and other anticholinergic effects, and movement disorders. Information about age-related differences in adverse events would be helpful, as would information about specific adverse effects, such as sedative, cardiovascular, loco-

motor, and anticholinergic effects of medicines. In addition, information about drug–disease interactions, such as deterioration of heart failure, is important.

Fourth, ageing is associated with changes in pharmacokinetic characteristics, such as a decrease in renal function and a relative increase in fat tissue. Hence, information about what steps should be taken to compensate for these differences is needed. For example, the reason for monitoring; the measures that should be monitored, e.g., renal function or coagulation parameters; when to start and when to stop monitoring; the frequency of monitoring; a critical value, such as a glomerular filtration rate below 30 ml/min; and the actions needed in such a situation, e.g., dose reduction.

Fifth, information about the convenience of medication use by patients, such as dosing instructions for older patients, but also the frequency of dosing and dosage forms, is important because medication adherence depends on these aspects.

Last, but not least, even if there are no differences in efficacy and safety between older and younger study participants, such information should be provided, to enable healthcare professionals to evaluate the strength of the evidence base in the older population.

TABLE 1 **Information needed for rational drug prescribing to older patients in summaries of product characteristics, product labels, and drug compendia**

Information topic	Specifications
Characteristics of the older study population	Number and proportion of study participants aged ≥75 years
	Exclusion criteria applied in clinical trials
Effectiveness in older population	Age-related differences in efficacy
	Age-related differences in dose response
	Time to benefit in older population (for chronic therapy)
Safety information in older population	Age-related differences in adverse effects
	Sedative effects
	Cardiovascular effects
	Locomotor effects
	Anticholinergic effects
Pharmacokinetic characteristics	Actions to be taken in older patients
	Why monitor
	What to monitor
	When to start and stop monitoring
	How frequently monitor
	Critical value
	How to respond
Convenience of use	Dosing instructions for older patients
	Frequency of dosing
	Available dosage forms

Criticasters might comment that the inclusion of the above-mentioned items will result in information overload and in unreadable documents that healthcare professionals do not have time to look through for relevant information. This might have been true for printed textbooks, but nowadays sources of drug information are available online and can be searched electronically, so that the need to condense information is no longer so relevant. Drug compendia that are widely used and those investigated in this thesis are available online.[65, 67, 68, 70, 71, 76] The way in which information is presented is vital – readability, comprehensibility, clinical relevance, and applicability are important to healthcare professionals.[77] Therefore, information should be grouped into topics and be concise, without loss of quality. Simple features, such as indexes at the top of the document with hyperlinks to subheadings, as applied in the US PL, increase the accessibility of information by removing the need to scroll through text. Information about older people could be grouped in one section, but the same information should also be presented in the pharmacokinetic section, safety section, et cetera. After all, the length of the document is less important than the ease of finding information. We suggest that drug information about older people should be included in widely used compendia, because older patients are prescribed medicines more often than any other population. A separate formulary for geriatric medicine is probably not useful because convenience of access and quick use are important factors in information-seeking in daily practice.[78-80]

Conclusion

Rational drug prescribing to older people remains a challenge for healthcare professionals, because the risk/benefit balance is often difficult to establish. Information to support rational drug prescribing is essential. The research presented in this thesis demonstrates that the evidence base of drug information, and the availability and applicability of such information, could be further improved. This will necessitate collaboration between relevant stakeholders throughout the life cycle of medicines.

References

1. Drenth-van Maanen AC. General introduction. Appropriate prescribing for older people. Enschede; 2013. p. 9-16.
2. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. *The Lancet* 2007; 370(9582):185-91.
3. Fitzsimmons PR, Blayney S, Mina-Corkill S, Scott GO. Older participants are frequently excluded from Parkinson's disease research. *Parkinsonism Relat Disord* 2012; 18(5):585-9.
4. Mitchell SL, Sullivan EA, Lipsitz LA. Exclusion of elderly subjects from clinical trials for Parkinson disease. *Arch Neurol* 1997; 54(11):1393-8.
5. Dodd KS, Saczynski JS, Zhao Y, Goldberg RJ, Gurwitz JH. Exclusion of older adults and women from recent trials of acute coronary syndromes. *J Am Geriatr Soc* 2011; 59(3):506-11.
6. Foerch C, Czapowski D, Misselwitz B, Steinmetz H, Neumann-Haefelin T, Arbeitsgruppe Schlaganfall Hessen (ASH). Gender imbalances induced by age limits in stroke trials. *Neuroepidemiology* 2010; 35(3):226-30.
7. Green P, Maurer MS, Foody JM, Forman DE, Wenger NK. Representation of older adults in the late-breaking clinical trials American Heart Association 2011 Scientific Sessions. *J Am Coll Cardiol* 2012; 60(9):869-71.
8. Kitzman DW, Rich MW. Age disparities in heart failure research. *JAMA* 2010; 304(17):1950-1.
9. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011; 171(6):550-6.
10. Yonemori K, Hirakawa A, Komiyama N, Kouno T, Ando M, Fujiwara Y, et al. Participation of elderly patients in registration trials for oncology drug applications in Japan. *Ann Oncol* 2010; 21(10):2112-8.
11. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004; 22(22):4626-31.
12. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: known problem, little progress. *J Clin Oncol* 2012; 30(17):2036-8.
13. Hutchins LF, Unger JM, Crowley JJ, Coltman Jr. CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999; 341(27):2061-7.
14. Clarfield AM, Friedman R. Survey of the age structure of "age-relevant" articles in four general medical journals. *J Am Geriatr Soc* 1985; 33(11):773-8.
15. Al-Refaie WB, Vickers SM, Zhong W, Parsons H, Rothenberger D, Habermann EB. Cancer trials versus the real world in the United States. *Ann Surg* 2011; 254(3):438-42.
16. Dowd R, Recker RR, Heaney RP. Study subjects and ordinary patients. *Osteoporos Int* 2000; 11(6):533-6.
17. Hori A, Shibata T, Kami M, Kusumi E, Narimatsu H, Kishi Y, et al. Age disparity between a cancer population and participants in clinical trials submitted as a new drug application of anticancer drugs in Japan. *Cancer* 2007; 109(12):2541-6.
18. Sharpe N. Clinical trials and the real world: selection bias and generalisability of trial results. *Cardiovasc Drugs Ther* 2002; 16(1):75-7.
19. Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry* 2002; 159(3):469-73.
20. Uijen AA, Bakx JC, Mokkink HG, van Weel C. Hypertension patients participating in trials differ in many aspects from patients treated in general practices. *J Clin Epidemiol* 2007; 60(4):330-5.

21. Beers E, van Puijenbroek EP, Bartelink IH, van der Linden CM, Jansen PA. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatraemia associated with valproic acid: Four case reports from the Netherlands and a case/non-case analysis of Vigibase. *Drug Saf* 2010; 33(1):47-55.
22. Beers E, Egberts TCG, Leufkens HGM, Jansen PAF. Information for adequate prescribing to older patients: An evaluation of the product information of 53 recently approved medicines. *Drugs Aging* 2013; Feb 19;30(4):255-62.
23. Beers E, Egberts TC, Leufkens HG, Jansen PA. The views of healthcare professionals, drug developers and regulators on information about older people needed for rational drug prescription. *PLoS One* 2013; 8(8):e72060.
24. European Medicines Agency. Studies in support of special populations: geriatrics ICH E7 (CPMP/ICH/379/95). (Accessed January 25, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002875.pdf).
25. EMA geriatric medicines strategy. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102291.pdf).
26. ICH topic E7 studies in support of special populations: geriatrics; questions and answers. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500005218.pdf).
27. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27(5):1047-53.
28. McMurdo M. Clinical research must include more older people. *BMJ* 2013; 346:f3899.
29. Curtin F, Schulz P. Assessing the benefit: risk ratio of a drug - randomized and naturalistic evidence. *Dialogues Clin Neurosci* 2011; 13(2):183-90.
30. Van Puijenbroek E, Conemans J, van Grootheest K. Spontaneous ADR reports as a trigger for pharmacogenetic research: a prospective observational study in the Netherlands. *Drug Saf* 2009; 32(3):255-64.
31. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta* 2003; 337(1-2):169-72.
32. Clayton JA, Le Jeune IR, Hall IP. Severe hyponatraemia in medical in-patients: aetiology, assessment and outcome. *QJM* 2006; 99(8):505-11.
33. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med* 2009; 122(9):857-65.
34. Bix L, de la Fuente J, Pimple KD, Kou E. Is the test of senior friendly/child resistant packaging ethical?. *Health Expect* 2009; 12(4):430-7.
35. Isaac LM, Tamblyn RM. Compliance and cognitive function: a methodological approach to measuring unintentional errors in medication compliance in the elderly. McGill-Calgary Drug Research Team. *Gerontologist* 1993; 33(6):772-81.
36. Atkin PA, Finnegan TP, Ogle SJ, Shenfield GM. Functional ability of patients to manage medication packaging: a survey of geriatric inpatients. *Age Ageing* 1994; 23(2):113-6.
37. Kairuz T, Bye L, Birdsall R, Deng T, Man L, Ross A, et al. Identifying compliance issues with prescription medicines among older people: a pilot study. *Drugs Aging* 2008; 25(2):153-62.
38. Kelly J, D'Cruz G, Wright D. Patients with dysphagia: experiences of taking medication. *J Adv Nurs* 2010; 66(1):82-91.
39. Nikolaus T, Kruse W, Bach M, Specht-Leible N, Oster P, Schlierf G. Elderly patients' problems with medication. An in-hospital and follow-up study. *Eur J Clin Pharmacol* 1996; 49(4):255-9.

40. Ostrom JR, Hammarlund ER, Christensen DB, Plein JB, Kethley AJ. Medication usage in an elderly population. *Med Care* 1985; 23(2):157-64.

41. Overgaard AB, Hojsted J, Hansen R, Moller-Sonnergaard J, Christrup LL. Patients' evaluation of shape, size and colour of solid dosage forms. *Pharm World Sci* 2001; 23(5):185-8.

42. Ruscin JM, Semla TP. Assessment of medication management skills in older outpatients. *Ann Pharmacother* 1996; 30(10):1083-8.

43. Tordoff J, Simonsen K, Thomson WM, Norris PT. "It's just routine." A qualitative study of medicine-taking amongst older people in New Zealand. *Pharm World Sci* 2010; 32(2):154-61.

44. Thwaites JH. Practical aspects of drug treatment in elderly patients with mobility problems. *Drugs Aging* 1999; 14(2):105-14.

45. Committee for medicinal products for human use (CHMP). Adequacy of guidance on the elderly regarding medicinal products for human use. (Accessed December 19, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500049541.pdf).

46. Website European Medicines Agency. (Accessed December 19, 2013, at http://www.ema.europa.eu/ema/).

47. European Federation of Pharmaceutical Industries and Associations (EFPIA). Position on drug development for older and ageing patients. (Accessed December 22, 2013, at http://www.efpia.eu/uploads/Modules/Documents/efpia-position-paper-geriatrics-11102013.pdf).

48. Diener L, Hugonot-Diener L, Alvino S, Baeyens JP, Bone MF, Chirita D, et al. Guidance synthesis. Medical research for and with older people in Europe: proposed ethical guidance for good clinical practice: ethical considerations. *J Nutr Health Aging* 2013; 17(7):625-7.

49. Website European Forum on Good Clinical Practice. (Accessed December 22, 2013, at http://www.efgcp.be/html.asp?what=AboutEFGCP.htm&L1=2&L2=0).

50. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomised controlled trials published in high-impact general medical journals: A systematic sampling review. *JAMA* 2007; 297(11):1233-40.

51. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310(20):2191-4.

52. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) – Module VIII – post-authorisation safety studies (EMA/813938/2011 Rev 1). (Accessed December 22, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf).

53. European Medicines Agency. The European paediatric initiative: History of the Paediatric Regulation. (Accessed December 22, 2013, at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/09/WC500003693.pdf.).

54. European Commission. Better medicines for children – from concept to reality. Progress report on the Paediatric Regulation ((EC) N°1901/2006). (Accessed December 22, 2013, at http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf).

55. Davies EH, Ollivier CM, Saint Raymond A. Paediatric investigation plans for pain: painfully slow! *Eur J Clin Pharmacol* 2010; 66(11):1091-7.

56. European Medicines Agency. 5-year Report to the European Commission - General report on the experience acquired as a result of the application of the Paediatric Regulation. (Accessed December 22, 2013, at http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf).

57. Antonov K, Brahm A, Carlsten A, de Joncheere K, Folino-Gallo P, Larsen L, et al. EUROMEDSTAT. The library of European Union pharmaceutical indicators: Expenditure and utilisation indicators March 2004.

58. McMurdo ME, Roberts H, Parker S, Wyatt N, May H, Goodman C, et al. Improving recruitment of older people to research through good practice. *Age Ageing* 2011; 40(6):659-65.

59. PREDICT Consortium. PREDICT charter for the rights of older people in clinical trials. (Accessed December 22, 2013, at http://www.predicteu.org/PREDICT_Charter/predict_charter.html).

60. Witham MD, McMurdo ME. How to get older people included in clinical studies. *Drugs Aging* 2007; 24(3):187-96.

61. Briggs R, Robinson S, O'Neill D. Ageism and clinical research. *Ir Med J* 2012; 105(9):311-2.

62. Bartlam B, Lally F, Crome P, Topinková E, Clarfield M, Cherubini A, et al. The PREDICT Study. Patients and carers views of older peoples participation in clinical trials. *European Geriatric Medicine* 2010; 1S:S1.

63. National Institute for Health Research (NIHR) Clinical Research Network. Website NIHR CRN. (Accessed September 20, 2013, at http://www.crncc.nihr.ac.uk/ppi.).

64. AGE Platform Europe. Website AGE Platform Europe. (Accessed December 22, 2013, at http://www.age-platform.eu/).

65. Health Care Insurance Board. Pharmacotherapeutic Compass. (Accessed July 3, 2013, at http://www.fk.cvz.nl/).

66. British National Formulary. London: Joint Formulary Committee. (Accessed January, 2013, at http://www.medicinescomplete.com).

67. PDR Network. Physicians' Desk Reference. (Accessed December 22, 2013, at http://www.pdr.net/).

68. European Commission. A guideline on summary of product characteristics. (Accessed December 22, 2013, at http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf).

69. Food and Drug Administration (FDA). Labeling for human prescription drug and biological products - Implementing the new content and format requirements – Draft guidance. (Accessed December 22, 2013, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf).

70. Belgian Centre for Pharmacotherapeutic Information (bcfi). Commented Drugs Directory and Folia Pharmacotherapeutica. (Accessed December 22, 2013, at http://www.bcfi.be/).

71. Rote Liste® Service GmbH. Rote Liste®. (Accessed December 22, 2013, at http://www.rote-liste.de/).

72. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of Risedronate on the Risk of Hip Fracture in Elderly Women. *N Engl J Med* 2001; 344(5):333-40.

73. Bulpitt CJ, Fletcher AE, Amery A, Coope J, Evans JG, Lightowlers S, et al. The Hypertension in the Very Elderly Trial (HYVET). *J Hum Hypertens* 1994; 8(8):631-2.

74. Shepherd J, Blauw GJ, Murphy MB, Bollen ELEM, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360(9346):1623-30.

75. Holmes HM, Min LC, Yee M, Varadhan R, Basran J, Dale W, et al. Rationalizing Prescribing for Older Patients with Multimorbidity: Considering Time to Benefit. *Drugs Aging* 2013; 30(9):655-66.

76. British National Formulary. London: Joint Formulary Committee. (Accessed January, 2013, at http://www.medicinescomplete.com).

77. Aronson JK. Drug interactions-information, education, and the British National Formulary. *Br J Clin Pharmacol* 2004; 57(4):371-2.

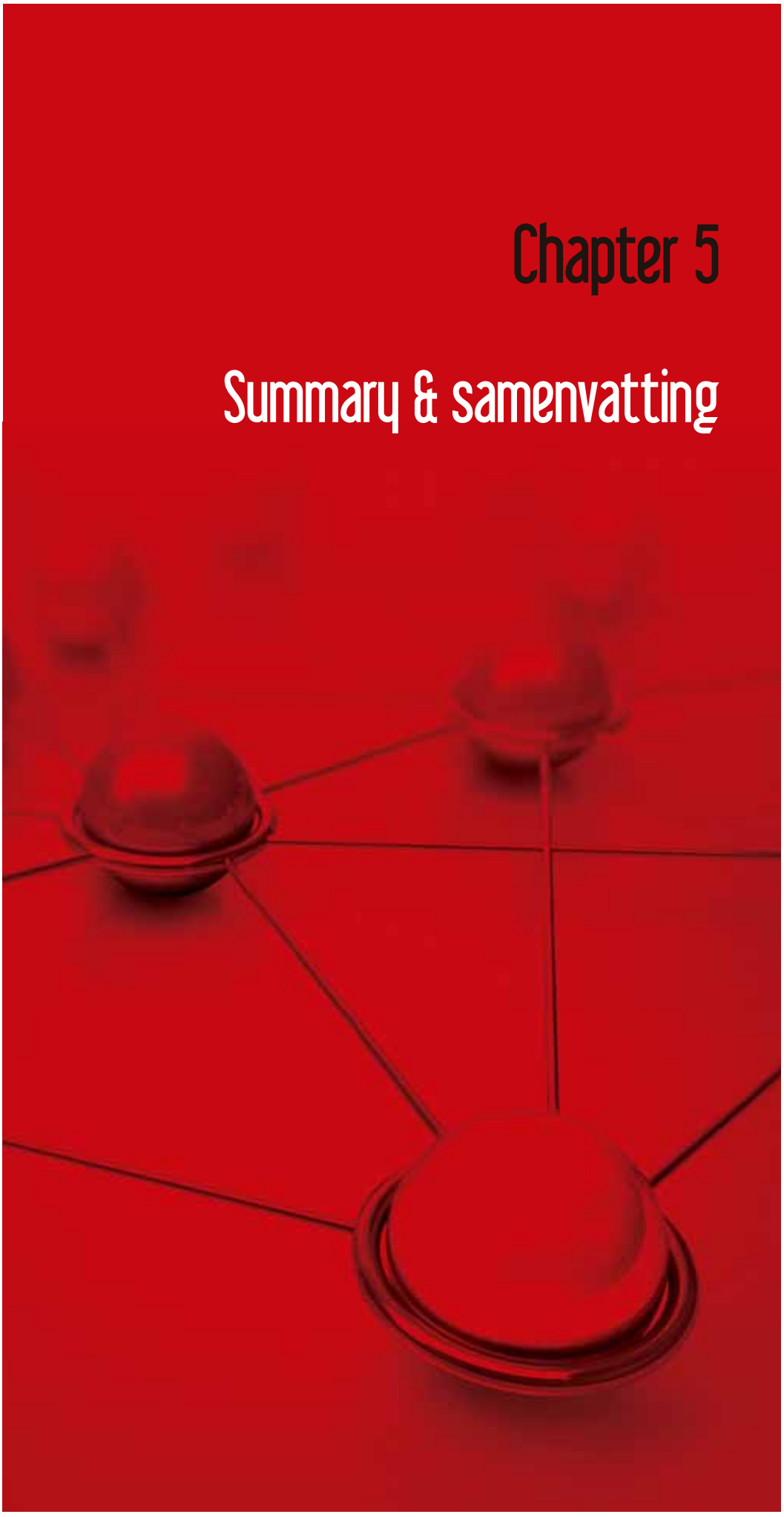
78. Northup DE, Moore-West M, Skipper B, Teaf SR. Characteristics of clinical information-searching: investigation using critical incident technique. *J Med Educ* 1983; 58(11):873-81.

79. Timpka T, Ekstrom M, Bjurulf P. Information needs and information seeking behaviour in primary health care. *Scand J Prim Health Care* 1989; 7(2):105-9.

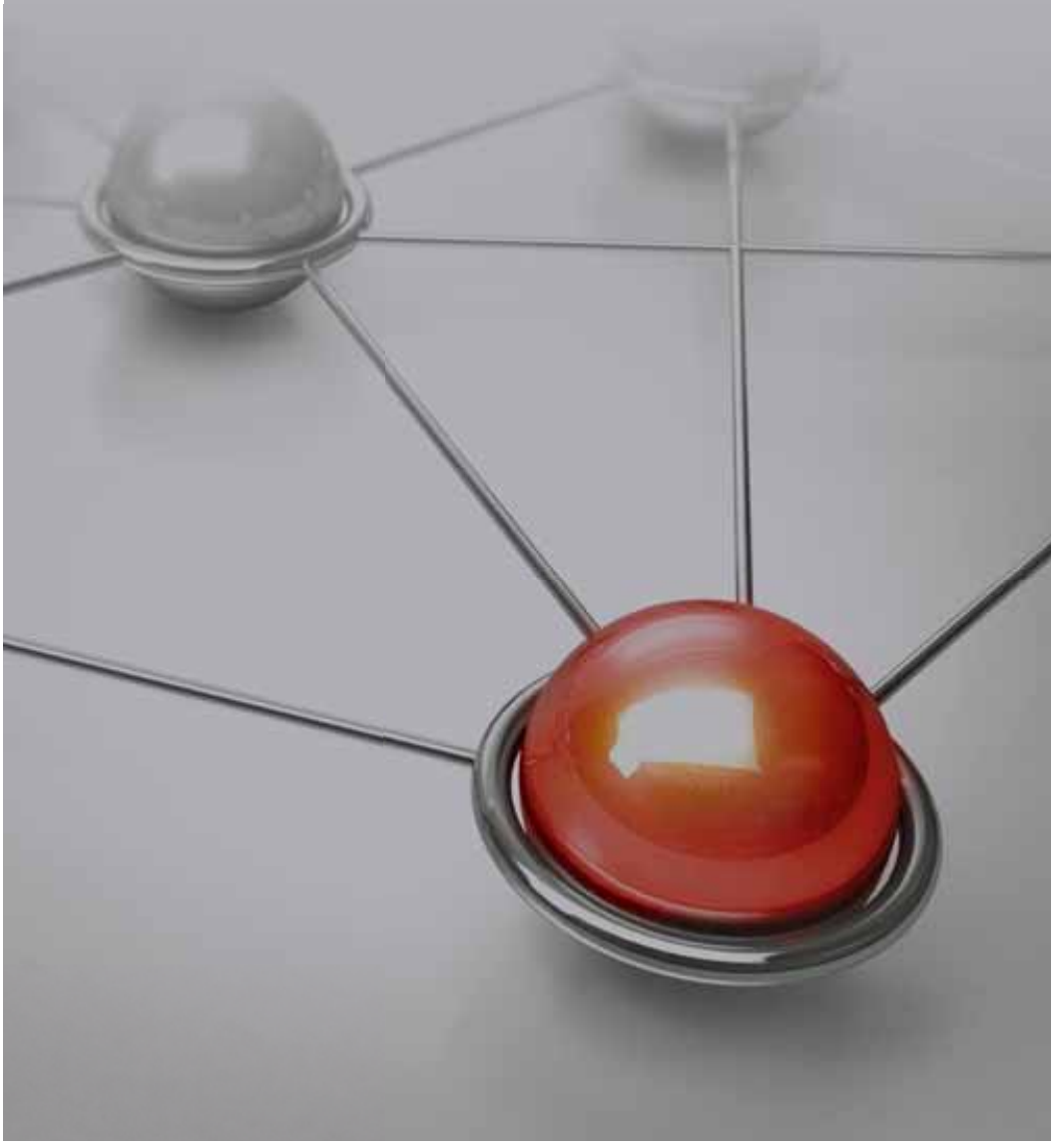
80. Dee C, Blazek R. Information needs of the rural physician: a descriptive study. *Bull Med Libr Assoc* 1993; 81(3):259-64.

Chapter 5

Summary & samenvatting



5.1
Summary



This thesis is entitled: Information for rational drug prescribing to older patients: availability and applicability. Rational drug prescribing is the process of making decisions about whether the benefits of a medicine outweigh the risks for the individual patient. This process is usually taken in relative uncertainty of the outcome in individual patients.

General introduction

Chapter 1 demonstrates that, with respect to older patients, rational drug prescribing is even more challenging, since older adults are at greater risk than younger adults of experiencing negative effects of medication. This increased risk is due to patient-related factors, such as the prevalence of multiple chronic conditions and treatment with several medicines; altered pharmacokinetic and pharmacodynamic characteristics; practical problems when using medication; and risk-increasing healthcare-related factors, such as errors in prescribing and dispensing medication, and inadequate communication between healthcare professionals.

To make the best possible decision about the benefit/risk balance of medicines for their older patients, healthcare professionals need drug information that is evidence based and applicable to their patients. To help them make these decisions, healthcare professionals often refer to drug compendia. The content of drug compendia originates for a major part from the European summaries of product characteristics (SmPCs) and US product labels (PLs), which are based on the application dossier. In turn, the application dossier describes, amongst other things, the efficacy and safety results of clinical trials performed during the pre-authorisation phase. It is important that these results are generalisable to older, often frail, patients in daily practice. It has long been recognised that the inclusion in clinical trials of older people who are representative of the target population in clinical practice could be improved. In 1994, European, US, and Japanese regulatory agencies and pharmaceutical industries, joint in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), published the E7 guideline for studies involving older patients. Besides the inclusion of older people in clinical trials, the collection of information on the effects of medicines in older patients during the post-marketing phase needs to be addressed, because the collection of data and information continues throughout the life cycle of a medicine.

Since older patients are at greater risk of adverse effects of medicines, and relatively little information is available about the effectiveness and safety of drugs in older people, the principal objective of the studies described in this thesis was to investigate the current status of information available to healthcare professionals to help them prescribe medication rationally to older people. The first aim was to investigate the availability and clinical applicability of information for healthcare professionals. The second aim was to analyse the evidence base of information originating from clinical practice.

The availability and applicability of information for rational drug prescribing to older patients

In Chapter 2.1, we investigated the participation of older people in pre-authorisation trials of recently approved medicines. In this way, we evaluated adherence to the ICH E7 guideline, which states that at least 50% of participants should be aged 65 years or older for medicines specifically indicated for older people and at least 100 subjects should be aged 65 years or older for medicines intended for younger and older people. From European public assessment reports (EPARs), published clinical trials, and the WHO International Clinical Trials Registry Platform, we extracted the number and proportion of randomised participants aged 65 years and older and 75 years and older, as well as information about the inclusion and exclusion criteria of studies of drugs for diseases characteristically associated with ageing (venous thromboembolism after replacement arthroplasty, osteoporosis, atrial fibrillation) and for diseases that are common in, but not unique to, older patients (type 2 diabetes mellitus, depression, bipolar disorder, epilepsy). The results of 114 phase II and III trials of 12 medicines showed that 43% of participants were aged 65 years and older and 16% 75 years and older. In trials involving diseases characteristically associated with ageing, 57% of subjects were aged 65 years and older and 22% were aged 75 years and older. Trials of three of five medicines for diseases not uniquely present in old age included more than 100 participants aged 65 years and older, as recommended by the ICH E7 guideline. However, the proportion of older people included in all these clinical trials (9% of subjects were aged ≥65 years) was much lower than the proportion of older people affected by these diseases in daily practice. Moreover, subjects older than 75 years comprised only 1% of the study population. Upper age limits were applied in 31% of the trials. The frequency of exclusion based on an upper age limit was significantly lower in trials involving diseases characteristically associated with ageing than in trials of diseases not unique to old age (18% vs. 45%; p=.002). Exclusion criteria were based on comorbidity (75%), concomitant medication (72%), and factors associated with advancing age (61%). These criteria were applied more frequently in larger trials (>500 participants; p<.02). We concluded that studies of diseases not uniquely associated with old age included an unacceptably low proportion of older people, much lower than the proportion of older people affected by these diseases in daily practice. Although the proportion of older participants in trials of diseases characteristically associated with ageing was appropriate for certain medicines, the use of age-sensitive exclusion criteria limited the representativeness of the trial population.

The limited representativeness of older people in clinical trials has a knock-on effect on the availability of relevant information from trials for healthcare professionals prescribing medicines to older individuals in daily clinical practice. The objective of the study presented in Chapter 2.2 was to investigate the availability, in the SmPCs of recently approved medicines, of information relevant to rational drug prescribing to older patients. We evaluated the SmPCs and EPARs of all non-generic medicines indicated for diseases that are common in older individuals and that were approved by the European Medicines Agency between January 2008 and December 2010. We considered the EPARs the second most complete, publicly available document after the application dossier, which is not available to the public.

Nineteen recommendations mentioned in the ICH E7 guideline were investigated for their availability in the SmPCs and EPARs of 53 medicines for diseases frequently present in older people. Information categories were the representation of, and clinical experience with, older people, as well as pharmacokinetic and drug–drug interaction studies. Information not included was classified as being essential or non-essential, based on the product characteristics. Overall, information on the ICH E7 items was available in 56% of the SmPCs (EPARs 79%); 41% of the SmPCs (EPARs 24%) did not provide information that should have been included. Twenty-seven percent of the SmPCs (EPARs 78%) provided information about the number of patients included. Moreover, only 2% of the SmPCs (EPARs 51%) provided information about the exclusion of patients with common comorbidities and only 14% (EPARs 81%) provided information about exclusion based on age. Thus, SmPCs, unlike EPARs, do not provide adequate information about older individuals. Consequently, it is not clear whether the information that is available about the efficacy and safety of a medicine is applicable to the frail older patients often seen in daily practice. The SmPC is intended for use by healthcare professionals in daily clinical practice and provides basic information required for safe and effective prescribing. As the EPAR describes regulatory considerations relevant to drug approval and is too long for daily use, the information about older individuals included in the SmPCs needs to be improved.

Drug compendia are mainly based on the SmPCs, and in the USA on the PLs, which are equivalent to the European SmPCs. As a result, if information relevant to rational drug prescribing to older patients is lacking in the SmPCs, then that information is probably also not included in drug compendia. In Chapter 2.3, we investigated the information provided about 35 medicines in the Belgian Repertorium, German Rote Liste, British National Formulary, Dutch Farmacotherapeutisch Kompas, and US Physician's Desk Reference (PDR, containing the Concise Monograph and the PL). The medicines were indicated for diseases common in older people, had a first European centralised approval between 2008 and 2011, and had been approved by the US Food and Drug Administration (FDA) before October 2012. A 19-item checklist, based on the ICH E7 guideline, was used to investigate the availability and, if relevant, clinical applicability of information about the studied population, clinical experience, pharmacokinetic properties, and drug–drug interactions of the medicines. Overall, 19% of information relevant to prescribing to older patients was available and applicable. The Belgian Repertorium provided the least information (7%) and the PDR the most (47%). Information about the nature of the studied population was provided least often (14%) and information about drug–drug interactions most often (49%). Most available information was applicable, except for information about age-related differences in adverse effects and the need for monitoring if patients had renal impairment. As a result, current European compendia, and to a lesser extent the PDR, do not provide sufficient clinically relevant information about medicines frequently prescribed to older patients. As these compendia are widely used to guide prescribing, the information about older individuals should be improved.

The question about what information is considered necessary for rational drug prescribing to older individuals in daily practice was studied in Chapter 2.4. The aim of the ICH E7 guideline is to improve knowledge about medicines that are prescribed to geriatric patients, but as it is a legislative document, it might not reflect the needs of healthcare professionals. Forty-

three European healthcare professionals, regulators, and drug developers with an interest in medication for older individuals were asked to what extent they thought healthcare professionals in daily practice need information about the representation of older patients in trials and about the pharmacokinetics, efficacy, safety, and convenience of use of medicines in older individuals. To this end, the participants were asked to complete a 29-item-questionnaire, with space for additional comments. In order to investigate the relevance of the items, five items were included in a second questionnaire, along with eleven control items. Median scores, differences between clinical and non-clinical respondents, and response consistency were analysed. As ten of eleven control questions were answered consistently,, the answers to all items of the first questionnaire and the five additional items were analysed. Thirty-seven (86%) respondents returned the first questionnaire and 84% (31 of 37) the second. Most participants considered it necessary to have information about age-related differences in adverse events, particularly locomotor effects and drug–disease interactions, dosing instructions for older people, and the proportion of individuals aged 65 years and older included in clinical trials. Clinicians considered information about the inclusion in clinical trials of participants aged 75 years or older, time to benefit in older people, anticholinergic effects, drug–disease interactions, and convenience of medicine use to be significantly more important than did non-clinical respondents. The study revealed that items considered necessary are currently not included in the ICH E7 guideline. Also, clinicians' and non-clinicians' opinions about the relevance of 15% of the items were significantly different. We concluded that all stakeholders should collaborate to improve the availability of information to support the rational prescribing of medicines to older individuals.

The evidence of information for rational drug prescribing to older patients

Chapter 3 focused on how information on the use of medicines by older patients in daily practice complements the evidence for rational drug prescribing to this population obtained from randomised clinical trials (RCTs). In Chapter 3.1, we compared evidence from RCTs with results from daily practice. The aims of this study were to evaluate the absolute risk of upper gastrointestinal (GI) events in general practice patients aged 65–74 years and 75 years and older who used non-selective NSAIDs (nsNSAIDs) and cyclooxygenase-2 inhibitors (coxibs), and to compare the magnitude of these risks with those reported in RCTs. We performed a retrospective cohort study and a descriptive comparison with RCTs, using records from the UK Clinical Practice Research Datalink (CPRD; from January 1995 to March 2013). Large RCTs (≥2000 patients) or meta-analyses of RCTs that compared coxibs with nsNSAIDs and which reported the incidence of upper GI events as primary outcome measure were included. Participants were patients aged 65 years and older with a prescription for an nsNSAID or a coxib, irrespective of exposure time, indication, or frequency of use. They were monitored for the occurrence of an upper GI event from the time of their first nsNSAID or coxib prescription. Main outcome measures were the incidence (events/1000 person–years) of upper GI events among nsNSAID and coxibs users aged 65–74 years and 75 years and older. The results showed that the incidence of upper GI events in the 714,224

patients included in the study was highest in first-time users and in patients who had used nsNSAIDs or coxibs on a daily basis for less than 6 months. The risk of upper GI events did not differ substantially between nsNSAID and coxibs users. A consistent age effect was seen in both medication groups. The reported incidence of events in nsNSAID users was 2.5–13.5 times higher in RCTs than in daily practice, and 19 times higher in subjects aged 75 years and older. For coxib users, the incidence of upper GI events was less than 5 times higher in RCTs than in daily practice, even among subjects aged 75 years and older. In conclusion, the frequency of upper GI events among older patients who use nsNSAIDs and coxibs was lower in general practice than might have been expected on the basis of results from RCTs. However, the incidence of upper GI events reported in RCTs was highly variable, and our research findings might have been affected by differences in baseline risks of the studied populations and by the way GI events were quantified. Despite these possible limitations, the study underlined the importance of observational studies in daily practice to complement what has been learned from RCTs.

Chapter 3.1 showed that studies performed in daily practice after market approval add to the evidence base for rational drug prescribing. The spontaneous reporting of suspected adverse drug reactions (ADRs) complements this knowledge. In Chapter 3.2, we reported on four cases of severe symptomatic hyponatraemia or syndrome of inappropriate antidiuretic hormone secretion (SIADH) in association with the use of valproic acid for which a causal relationship was suspected. Four women aged 57, 67, 71, and 88 years developed symptomatic hyponatraemia or SIADH after starting valproic acid. Despite concomitant medication or comorbidity, a causal relationship was plausible. The strength of this association was established in a case/non-case analysis between cases of hyponatraemia and the use of valproic acid reported to Vigibase, the ADR database of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre. The reporting odds ratio, adjusted for possible confounding by concomitant medication, was calculated and revealed that valproic acid use was disproportionally associated with hyponatraemia and SIADH (corrected reporting odds ratio 1.83, 95% confidence interval 1.61, 2.08). On the basis of the described cases and the reports in Vigibase, it is likely that there is a causal relationship between valproic acid use and hyponatraemia or SIADH, but the mechanism by which valproic acid causes hyponatraemia or SIADH is not known. Valproic acid use could lead to a reduced sensitivity of hypothalamic osmoreceptors, or the drug could directly affect renal tubular function, thereby leading to SIADH. Thus a combination of effects on the osmoreceptors and a lack of compensation of the salt-water imbalance by nephrons causes SIADH in some patients using valproic acid. It could be a dose- or concentration-related adverse effect. This study not only doubled the number of published cases of valproic acid ADRs, but was also supported by the data from Vigibase regarding the presence of such an association. Thus the spontaneous reporting of suspected adverse effects is a valuable way to fill the knowledge gap in the post-marketing phase.

Other information that can be obtained about the use of medicines in daily practice concerns how older patients use their medications. Chapter 3.3 presents a qualitative study that aimed to identify the practical problems that older people experience when taking their medicines and how they manage these problems. An additional aim was to determine the potential

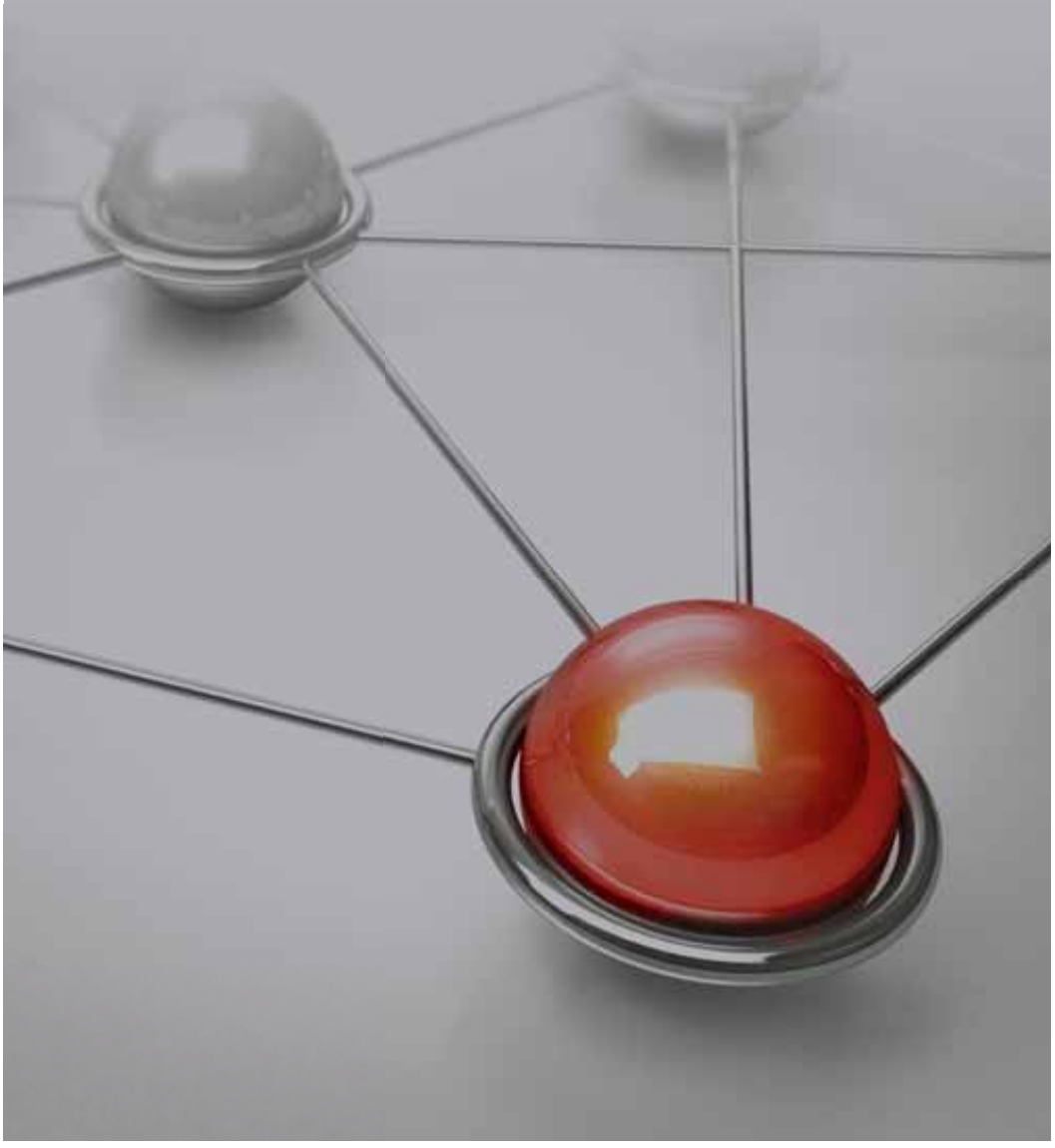
clinical relevance of these problems. We performed semi-structured face-to-face interviews in a community pharmacy and on a geriatric outpatient ward in Utrecht, the Netherlands. Participants were 59 community-dwelling people aged 70 years or older who used at least three different oral prescription medicines daily and managed their medication independently. We identified 211 practical problems and 184 strategies to manage these problems. Fifty-six (95%) participants experienced one or more practical problem, ranging from problems with reading and understanding the instructions for use, handling the outer packaging, handling the immediate packaging, completing any preparation prior to use, and taking the medicine. In ten participants at least one of their problems, in combination with the strategy to resolve the problem, was considered to have potential clinical consequences, and eleven (5%) problems were considered to potentially cause moderate or severe deterioration of the patient's clinical condition. In conclusion, older people experience a number of problems when using their medicines, and these problems can lead to incorrect medication use, with potentially clinically relevant consequences. This study provided a classification of the practical problems experienced by older people. The findings represent a challenge to healthcare professionals, drug developers, and regulators to find ways to diminish the practical problems experienced by older people.

General discussion

In Chapter 4, the results of the individual studies are discussed and put into a broader perspective. We focused on the evidence, availability, and applicability of information needed for rational drug prescribing to older people, and the implications our findings have for policy and daily practice. As shown in Chapter 2, the availability and applicability of information relevant to rational drug prescribing to older people in SmPCs, PLs, and drug compendia can be improved. In addition, information considered necessary by healthcare professionals is currently not collected in pre-approval studies. In order to prescribe rationally to older patients, the information about drugs gathered during the pre-approval and post-approval phases needs to be relevant for, and applicable to, older patients in daily practice. Moreover, this information should be adequately reflected in SmPCs, PLs, and drug compendia. As shown in Chapter 3 of this thesis, information gained in daily practice is a valuable complement to the findings of studies performed in the pre-authorisation phase. With respect to older people, it appears important to know more about safety measures and about the practical use of medicines. It will only be possible to improve the information available to support rational drug prescribing to older patients if all parties work together to increase knowledge about medicines and their use.

5.2

Samenvatting



Dit proefschrift draagt de titel: Informatie voor het rationeel voorschrijven van geneesmiddelen aan ouderen: beschikbaarheid en toepasbaarheid. Een geneesmiddel wordt op rationele wijze voorgeschreven als de voordelen van een geneesmiddel afgewogen worden tegen de risico's voor de individuele patiënt. Bij deze afweging is het meestal niet helemaal zeker wat het effect zal zijn voor de individuele patiënt.

Algemene inleiding

Hoofdstuk 1 laat zien dat het rationeel voorschrijven van geneesmiddelen aan oudere patiënten een nog grotere uitdaging is dan het voorschrijven aan jongere volwassenen. Ouderen van 65 jaar en ouder, maar vooral mensen boven de leeftijd van 75 jaar, lopen namelijk een groter risico dan jongere volwassenen op het ervaren van negatieve effecten van medicatie. Dit verhoogde risico is ten eerste het gevolg van patiëntgebonden factoren. Deze factoren zijn het tegelijkertijd voorkomen van verschillende chronische aandoeningen en de behandeling met verschillende medicijnen, een veranderde reactie van het lichaam op het geneesmiddel (farmacokinetiek genoemd) en praktische problemen tijdens het gebruik van geneesmiddelen. Het risico op negatieve effecten wordt daarnaast verhoogd door zorg-gerelateerde factoren, zoals fouten in het voorschrijven of toedienen van medicatie en een gebrekkige communicatie tussen zorgverleners.

Om een zo goed mogelijke afweging te kunnen maken van de voordelen en de risico's van geneesmiddelen voor oudere patiënten hebben zorgverleners informatie nodig. Deze informatie moet beschikbaar zijn en toepasbaar zijn op de oudere patiënt. Bij het rationeel voorschrijven kunnen zorgverleners geneesmiddelhandboeken raadplegen. Zulke handboeken nemen veel informatie over van de samenvatting van de productkenmerken (SmPC) en van het Amerikaanse product label (PL). De SmPC en het PL bevatten onder andere informatie voor de zorgverlener over de werking en de bijwerkingen van het geneesmiddel en de juiste dosering bij kinderen, volwassenen en ouderen. De SmPC en het PL halen deze informatie uit het registratiedossier. Dit dossier beschrijft alle onderzoeken die zijn verricht tijdens de ontwikkeling van het geneesmiddel. Ook de klinische onderzoeken met mensen staan erin beschreven. Het registratiedossier is niet openbaar, maar wordt beoordeeld door de registratie-autoriteiten. Deze wegen af of een geneesmiddel kan worden toegelaten tot de markt.

De resultaten van de klinische onderzoeken die vóór toelating tot de markt worden uitgevoerd moeten toepasbaar zijn op patiënten in de dagelijkse praktijk, die vaak ouder en kwetsbaarder zijn dan de onderzochte mensen. Sinds de jaren 1980 bleek dat meer ouderen uit de dagelijkse praktijk zouden moeten deelnemen in de klinische onderzoeken. Daarom heeft in 1994 de Internationale Conferentie voor Harmonisatie van Technische Voorschriften voor de Registratie van Farmaceutische Producten voor Menselijk Gebruik (ICH) de E7 richtlijn gepubliceerd. Deze richtlijn geeft aan dat meer ouderen moeten worden onderzocht in klinische onderzoeken voordat een geneesmiddel op de markt komt. Ook moet na toelating tot de markt blijvend kennis worden verzameld over het effect van geneesmiddelen bij ouderen in de dagelijkse praktijk. Het verbeteren van de kennis over de veiligheid en effectiviteit van

geneesmiddelen is immers een proces dat tijdens de gehele bestaanscyclus van een geneesmiddel doorgaat.

Het overkoepelende doel van dit proefschrift is om de huidige status van informatie voor professionals in de gezondheidszorg te onderzoeken om hen te helpen medicatie rationeel voor te schrijven aan oudere patiënten. Dit aangezien oudere patiënten een groter risico lopen op negatieve effecten naast een relatief tekort aan informatie over de werkzaamheid en veiligheid van geneesmiddelen bij oudere mensen. We onderzochten ten eerste in hoeverre informatie voor zorgverleners beschikbaar is en toepasbaar is op oudere patiënten. Ten tweede analyseerden we of de informatie uit de dagelijkse praktijk overeenkomt met de kennis die is opgedaan tijdens de klinische onderzoeken.

De beschikbaarheid en toepasbaarheid van informatie voor het rationeel voorschrijven van geneesmiddelen aan oudere patiënten

In hoofdstuk 2.1 onderzochten we de deelname van ouderen in klinische onderzoeken vóór de registratie van recent goedgekeurde geneesmiddelen. Op deze manier konden we ook evalueren in hoeverre de ICH E7 richtlijn werd nageleefd. In de ICH E7 richtlijn staat dat ten minste 50% van de deelnemers 65 jaar of ouder moet zijn in onderzoeken van geneesmiddelen die specifiek voor ouderen zijn bedoeld. Daarnaast moeten meer dan 100 proefpersonen ouder dan 65 jaar zijn in onderzoeken van geneesmiddelen die bestemd zijn voor jongere èn oudere mensen. We onderzochten het aantal en het percentage deelnemers met een leeftijd van 65 jaar en 75 jaar en ouder. Daarnaast analyseerden we alle uitsluitingscriteria van onderzoeken van geneesmiddelen voor ziekten die vooral voorkomen op oudere leeftijd (veneuze trombo-embolie na heup- of knievervangende operaties, botontkalking en boezemfibrilleren) en ziekten die veel voorkomen bij, maar niet uniek zijn voor, oudere patiënten (diabetes mellitus type 2, depressie, bipolaire stoornis en epilepsie).

Er waren 114 onderzoeken verricht voor de registratie van 12 geneesmiddelen. In alle onderzoeken samen was 43% van de deelnemers 65 jaar of ouder; 16% was 75 jaar of ouder. Zeven van de 12 geneesmiddelen waren bedoeld voor ziekten die specifiek voorkomen op oudere leeftijd. In die onderzoeken was iets meer dan de helft 65 jaar of ouder, zoals in de ICH E7 richtlijn staat aangegeven, en bijna een kwart was minimaal 75 jaar. De andere 5 geneesmiddelen waren bedoeld voor ziekten die bij oudere en jongere volwassenen voorkomen. In de onderzoeken van 3 van die 5 geneesmiddelen werden meer dan 100 deelnemers van 65 jaar en ouder onderzocht, zoals aangegeven staat in de ICH E7 richtlijn. Hoewel dat aantal volgens de regels hoog genoeg was, was het percentage ouderen in die onderzoeken maar 9%. Slechts 1% van de deelnemers was minimaal 75 jaar. Dit is veel lager dan het percentage ouderen dat in de dagelijkse praktijk aan deze ziekten lijdt en deze geneesmiddelen krijgt voorgeschreven.

In een-derde van de onderzoeken werden ouderen uitgesloten van deelname op basis van hun leeftijd. Dat kwam aanzienlijk vaker voor in onderzoeken van geneesmiddelen die bedoeld

zijn voor jongere en oudere patiënten (45%), ten opzichte van onderzoeken van geneesmiddelen voor ziekten die voornamelijk op oudere leeftijd voorkomen (18%). In driekwart van de onderzoeken werden mensen uitgesloten van deelname als ze gelijktijdig andere ziekten hadden of andere medicatie gebruikten. Andere uitsluitingscriteria die vooral de deelname van ouderen treffen, zoals het niet zelf kunnen ondertekenen van het toestemmingformulier of communicatieproblemen, werden in meer dan de helft van de onderzoeken gebruikt.

We concludeerden dat onderzoeken van geneesmiddelen voor ziekten die voorkomen bij jongere en oudere volwassenen een onaanvaardbaar laag percentage ouderen onderzoeken. Het percentage ligt veel lager dan het aandeel ouderen dat lijdt aan deze ziekten in de dagelijkse praktijk. In onderzoeken van geneesmiddelen voor ziektes die vooral op oudere leeftijd voorkomen was het percentage ouderen voor een aantal geneesmiddelen voldoende. Toch zorgden de uitsluitingscriteria ervoor dat de onderzoekspopulatie niet representatief is voor de groep oudere patiënten in de dagelijkse praktijk.

De beperkte representativiteit van ouderen in klinische onderzoeken heeft gevolgen voor de beschikbaarheid van relevante informatie voor zorgverleners in de dagelijkse praktijk. Het doel van het onderzoek in hoofdstuk 2.2 was om de beschikbaarheid van informatie voor het rationeel voorschrijven van geneesmiddelen aan oudere patiënten te onderzoeken in de SmPC's van de onlangs goedgekeurde geneesmiddelen. Van 53 geneesmiddelen voor ziekten die veel voorkomen bij oudere personen en die tussen januari 2008 en december 2010 waren goedgekeurd door de Europese Registratie-autoriteit (EMA) evalueerden we de SmPC's en de Europese openbare beoordelingsrapporten (EPARs). Deze EPARs bevatten de overwegingen van de EMA tijdens het proces van al dan niet toelaten van een geneesmiddel tot de markt. Omdat de EPAR delen bevat van het registratiedossier, beschouwden we de EPAR als het meest complete openbare document, na het niet-openbare registratiedossier. Negentien onderwerpen die in de ICH E7 richtlijn worden beschreven werden onderzocht op hun beschikbaarheid in de SmPC's en EPARs. Deze onderwerpen konden we indelen in vier categorieën: de vertegenwoordiging van oudere mensen in klinische onderzoeken, de ervaringen met het geneesmiddel in oudere mensen, farmacokinetische onderzoeken en onderzoeken naar geneesmiddelinteracties.

In totaal was informatie over iets meer dan de helft van de onderwerpen uit de ICH E7 richtlijn beschikbaar in de SmPC's; in de EPARs was dit bijna 80%. Meer dan 40% van de essentiële informatie ontbrak in de SmPC's (EPARs 24%). Informatie over het aantal oudere patiënten werd genoemd in 27% van de SmPC's, ten opzichte van 78% van de EPARs. Bovendien werd in 2% van de SmPC's (EPARs 51%) informatie verstrekt over het uitsluiten van patiënten met andere ziekten dan het onderzochte ziektebeeld. Veertien procent van de SmPC's, maar 81% van de EPARs verstrekte informatie over uitsluiting op basis van leeftijd.

Deze resultaten leiden tot de conclusie dat de SmPC's, in tegenstelling tot de EPARs, onvoldoende informatie beschikbaar stellen aan zorgverleners die relevant is voor het rationeel voorschrijven aan ouderen. Daarnaast is het niet duidelijk of de beschikbare informatie in de SmPC toepasbaar is op de kwetsbare oudere patiënt in de dagelijkse praktijk.

Handboeken over geneesmiddelen zijn voornamelijk gebaseerd op de SmPC's, en in de VS op de PL, die gelijkwaardig is aan de Europese SmPC. Wanneer informatie voor het rationeel voorschijven van geneesmiddelen aan oudere patiënten ontbreekt in de SmPC, kan dit een negatief effect hebben op de beschikbaarheid van dergelijke informatie in handboeken. In hoofdstuk 2.3 onderzochten we de beschikbare informatie over 35 geneesmiddelen in de volgende handboeken: het Belgische Repertorium, de Duitse Rote Liste, de Britse National Formulary, het Nederlandse Farmacotherapeutisch Kompas en de Amerikaanse Physician's Desk Reference (PDR, met daarin de beknopte monografie en het PL). De onderzochte geneesmiddelen waren bedoeld voor ziekten die vaak voorkomen bij oudere mensen en hadden een eerste Europese gecentraliseerde goedkeuring tussen 2008 en 2011 en een goedkeuring van de Amerikaanse Food and Drug Administration (FDA) voor oktober 2012. De 19 onderwerpen uit de ICH E7 richtlijn werden weer gebruikt om de beschikbaarheid van informatie te onderzoeken en, indien relevant, de klinische toepasbaarheid van de informatie voor de vier categorieën (de onderzochte populatie, de klinische ervaring, farmacokinetische eigenschappen en interacties tussen geneesmiddelen).

In totaal was 19% van de informatie die relevant is voor het rationeel voorschrijven aan oudere patiënten beschikbaar en toepasbaar. Het Belgische Repertorium verstrekte de minste informatie (7%), de PDR de meeste (47%). Informatie over de aard van de onderzochte populatie werd het minst vaak verstrekt (14%) en informatie over geneesmiddelinteracties het vaakst (49%). Als informatie beschikbaar was, dan was die in de meeste gevallen ook toepasbaar. Dit gold echter niet voor informatie over leeftijdsgebonden verschillen in bijwerkingen en over de noodzaak tot controle bij nierinsufficiëntie.

We concludeerden dat in de huidige situatie de Europese handboeken, en in mindere mate de Amerikaanse PDR, onvoldoende klinisch relevante informatie bevatten over medicijnen die vaak voorgeschreven worden aan oudere patiënten. Omdat deze handboeken op grote schaal worden gebruikt bij de besluitvorming tot het voorschrijven van geneesmiddelen, is het noodzakelijk de beschikbaarheid van informatie te verbeteren.

De vraag welke informatie voor het rationeel voorschrijven van geneesmiddelen aan oudere patiënten in de dagelijkse praktijk noodzakelijk wordt geacht werd bestudeerd in hoofdstuk 2.4. De ICH E7 richtlijn is opgesteld door de registratie-autoriteiten en de farmaceutische industrie. Mogelijk beantwoordt de richtlijn niet aan de behoeften van zorgverleners. Aan 43 Europese zorgverleners, toezichthouders en professionals uit de farmaceutische industrie met een interesse in medicijnen voor oudere personen werden twee vragenlijsten gestuurd. Zij beantwoordden de vraag in hoeverre in de dagelijkse praktijk zorgverleners behoefte hebben aan informatie over: de vertegenwoordiging van oudere patiënten in klinische onderzoeken, farmacokinetiek, werkzaamheid, veiligheid en gebruiksgemak van geneesmiddelen door oudere patiënten. De eerste enquête bestond uit 29 vragen, met ruimte voor toevoegingen. De tweede vragenlijst bestond uit 11 vragen uit de eerste enquête, ter controle, en vijf nieuwe vragen die waren voorgesteld door de deelnemers in de eerste ronde. We onderzochten de gemiddelde scores en de verschillen tussen klinische en niet-klinische deelnemers. Klinische deelnemers waren zorgverleners betrokken bij patiëntenzorg en niet-klinische deelnemers

waren de toezichthouders en de professionals uit de farmaceutische industrie. In 10 van de 11 controlevragen waren de antwoorden vergelijkbaar tussen de vragenlijsten.

Zevenendertig (86%) deelnemers beantwoordden de eerste vragenlijst, 31 van de 37 deelnemers (84%) de tweede. De meeste deelnemers vonden de volgende informatie noodzakelijk: leeftijdsgebonden verschillen in bijwerkingen, vooral negatieve effecten op de beweging (spieren, botten) en effecten van geneesmiddelen op andere ziektes, doseringsinstructies voor oudere mensen en het percentage ouderen van 65 jaar en ouder dat deelgenomen heeft aan klinische onderzoeken. Zorgverleners vonden de volgende informatie significant belangrijker dan niet-zorgverleners: informatie over de het aantal deelnemers van 75 jaar of ouder aan klinische onderzoeken, de *time to benefit* van geneesmiddelen (dit is de tijd totdat een geneesmiddel effect heeft op de lange termijn), anticholinerge bijwerkingen (zoals wazig zien, achteruitgang van het denkvermogen, gestoorde blaaslediging), effecten van geneesmiddelen op andere ziektes en het gebruiksgemak van het geneesmiddel voor de oudere patiënt.

Het onderzoek toonde aan dat onderwerpen die noodzakelijk geacht werden momenteel niet opgenomen zijn in de ICH E7 richtlijn. Ook verschilden de meningen van zorgverleners en niet-zorgverleners op 15% van de onderwerpen. Om die redenen hebben we geconcludeerd dat alle zorgverleners, toezichthouders en professionals uit de farmaceutische industrie moeten samenwerken om de beschikbaarheid van informatie voor het rationeel voorschrijven aan oudere mensen te verbeteren.

De bewijskracht van kennis uit de dagelijkse praktijk voor het rationeel voorschrijven van geneesmiddelen aan oudere patiënten

In hoofdstuk 3.1 vergeleken we de resultaten uit gerandomiseerde klinische onderzoeken (RCT's), waarin patiënten willekeurig het ene of het andere geneesmiddel krijgen, met resultaten uit de dagelijkse praktijk bij patiënten van 65-74 jaar en patiënten van 75 jaar en ouder. Hiervoor onderzochten we het risico op bijwerkingen in het bovenste gedeelte van het maagdarmkanaal, zoals maagzweren en -bloedingen, tijdens gebruik van twee soorten veelgebruikte pijnstillers, namelijk niet-selectieve NSAID's (nsNSAID's, zoals diclofenac en ibuprofen) en cyclo-oxygenase-2-remmers (coxibs, zoals celecoxib en etoricoxib). Hiervoor maakten we gebruik van patiëntgegevens uit de grootste huisartsendatabank ter wereld, de Briste Clinical Practice Research Datalink (CPRD). Alle mensen van 65 jaar en ouder die tussen januari 1995 en maart 2013 een recept kregen voor een nsNSAID of een coxib werden gevolgd om te bepalen of zij een bijwerking kregen in het bovenste gedeelte van het maagdarmkanaal. Het maakte niet uit wat de duur van de behandeling was, de reden van voorschrijven of de frequentie van het gebruik. Het tweede doel was om de hoogte van het risico in de dagelijkse praktijk te vergelijken met de risico's die zijn gerapporteerd in RCT's. Hiervoor analyseerden we grote RCT's (≥2000 patiënten) of meta-analyses van RCT's die coxibs met nsNSAIDs vergeleken en die de frequentie van optreden van bijwerkingen in het bovenste gedeelte van het maagdarmkanaal onderzochten.

In de CPRD databank volgden we meer dan 714 duizend patiënten. De resultaten toonden aan dat het risico op bijwerkingen in het bovenste gedeelte van het maagdarmkanaal het hoogst waren tijdens het eerste recept en bij patiënten die dagelijks nsNSAIDs of coxibs gebruikten gedurende minder dan 6 maanden. Het risico op deze bijwerkingen verschilde niet wezenlijk tussen nsNSAID- en coxib-gebruikers. Het risico was duidelijk hoger voor de groep patiënten van 75 jaar en ouder. In de RCT's was het risico op bijwerkingen in het bovenste gedeelte van het maagdarmkanaal bij nsNSAID-gebruikers 2,5 tot 13,5 maal hoger in vergelijking met de dagelijkse praktijk. Bij proefpersonen van 75 jaar en ouder was dit risico 19 keer hoger. Voor coxib-gebruikers was het risico in RCT's minder dan 5 keer hoger, ook voor ouderen van 75 jaar en ouder.

Kortom, de frequenties van bijwerkingen in het bovenste gedeelte van het maagdarmkanaal bij oudere patiënten die nsNSAIDs en coxibs in de huisartspraktijk gebruiken was lager dan werd gesuggereerd door de bevindingen van de RCT's. Echter, de gevonden risico's in de RCT's varieerde sterk. Onze onderzoeksresultaten kunnen bovendien zijn beïnvloed door verschillen in de uitgangssituatie van de bestudeerde ouderen en in de manier waarop de bijwerkingen werden aangetoond. Ondanks deze mogelijke beperkingen onderstreept dit onderzoek het belang van onderzoeken in de dagelijkse praktijk als aanvulling op wat er is gevonden in RCT's.

Zoals hoofdstuk 3.1 laat zien voegen onderzoeken in de dagelijkse praktijk, na goedkeuring van een geneesmiddel tot de markt, relevante kennis toe voor het rationeel voorschrijven van geneesmiddelen. Ook meldingen van vermoede bijwerkingen vormen een aanvulling hierop. In hoofdstuk 3.2 beschrijven wij vier gevallen van een ernstig verlaagd zoutgehalte in het bloed (hyponatriëmie) of het syndroom van inadequate afgifte van het hormoon dat de vorming van urine tegengaat (SIADH) tijdens het gebruik van valproïnezuur.

Vier oudere vrouwen van 57, 67, 71 en 88 jaar ontwikkelden klachten van hyponatriëmie of SIADH na het starten van valproïnezuur. Ondanks gelijktijdig gebruik van andere medicatie of andere ziektes was een oorzakelijke relatie met valproïnezuur aannemelijk. De sterkte van deze relatie werd bevestigd door een analyse van gemelde gevallen van hyponatriëmie en SIADH en het gebruik van valproïnezuur in Vigibase, de bijwerkingendatabank van de Wereldgezondheidsorganisatie (WHO). Meldingen van valproïnezuur waren onevenredig vaak gerelateerd aan hyponatriëmie en SIADH. Op basis van de beschreven gevallen en de meldingen in Vigibase kan een oorzakelijk verband tussen het gebruik van valproïnezuur en hyponatriëmie of SIADH worden vermoed. Het mechanisme waardoor valproïnezuur hyponatriëmie en SIADH kan veroorzaken is niet volledig duidelijk. In het artikel beschrijven we een aantal mogelijke verklaringen.

Met het onderzoek verdubbelde niet alleen het aantal gepubliceerde gevallen, ook de gegevens van Vigibase onderschrijven het oorzakelijke verband. Spontane meldingen van vermoede bijwerkingen vormen een waardevolle manier om de kenniskloof in de post-marketing fase te vullen.

Bewijs uit de dagelijkse praktijk wordt ook gevormd door de ervaring met medicijnen door oudere patiënten. Hoofdstuk 3.3 geeft een onderzoek weer dat gericht is op het identificeren van praktische problemen die oudere mensen ervaren bij het gebruik van hun medicijnen. Daarnaast onderzochten we de wijze waarop de deelnemers deze problemen oplossen en we bepaalden de potentiële klinische relevantie daarvan. We voerden semigestructureerde face-to-face interviews uit met ouderen uit een openbare apotheek en van een geriatrische poliklinische afdeling in Utrecht. Deelnemers waren 59 thuiswonende mensen van 70 jaar of ouder die dagelijks ten minste drie verschillende orale geneesmiddelen op recept gebruikten en zelfstandig hun medicatie beheerden.

Wij identificeerden 211 praktische problemen en 184 manieren om met deze problemen om te gaan. Zesenvijftig deelnemers (95%) ervoeren een of meer praktische problemen. Deze problemen varieerden van problemen met het lezen en begrijpen van de instructies voor het gebruik, het uit het doosje halen van de medicatie, het uit de blister of pot halen van geneesmiddelen, het breken van een geneesmiddel en het innemen van het medicijn. Bij 10 van de 59 deelnemers bestond de kans dat de oplossing voor het ervaren probleem zou leiden tot verslechtering van de gezondheid, zoals het niet innemen van maagbeschermende medicatie omdat de deelnemer de bijwerkingen in de bijsluiter te verontrustend vond. Elf (5%) problemen werden beschouwd als leidend tot mogelijk matige of ernstige klinische verslechtering.

Al met al kunnen bij ouderen praktische problemen bij het gebruik van hun medicijnen leiden tot een onjuist gebruik van hun medicatie, met mogelijk klinisch relevante gevolgen. De bevindingen vormen een uitdaging voor zorgverleners, de farmaceutische industrie en toezichthouders om manieren te vinden om de praktische problemen van ouderen te verminderen.

Algemene discussie

In hoofdstuk 4 worden de resultaten van de afzonderlijke onderzoeken besproken en in een breder perspectief geplaatst. Daarbij richten we ons op de beschikbaarheid en de toepasbaarheid van informatie voor het rationeel voorschrijven van geneesmiddelen aan oudere patiënten en op de bewijskracht die de dagelijkse praktijk levert. Ook bespreken we de aanbevelingen die voortvloeien uit dit proefschrift voor het beleid en de dagelijkse praktijk.

Zoals aangegeven in hoofdstuk 2 kunnen de beschikbaarheid en de toepasbaarheid van informatie voor het rationeel voorschrijven van geneesmiddelen aan oudere patiënten verbeterd worden. Dit geldt voor de SmPC's, PLs en de handboeken. Daarnaast is het van belang dat informatie die relevant is voor zorgverleners zoveel mogelijk wordt verzameld vóór toelating van een geneesmiddel tot de markt.

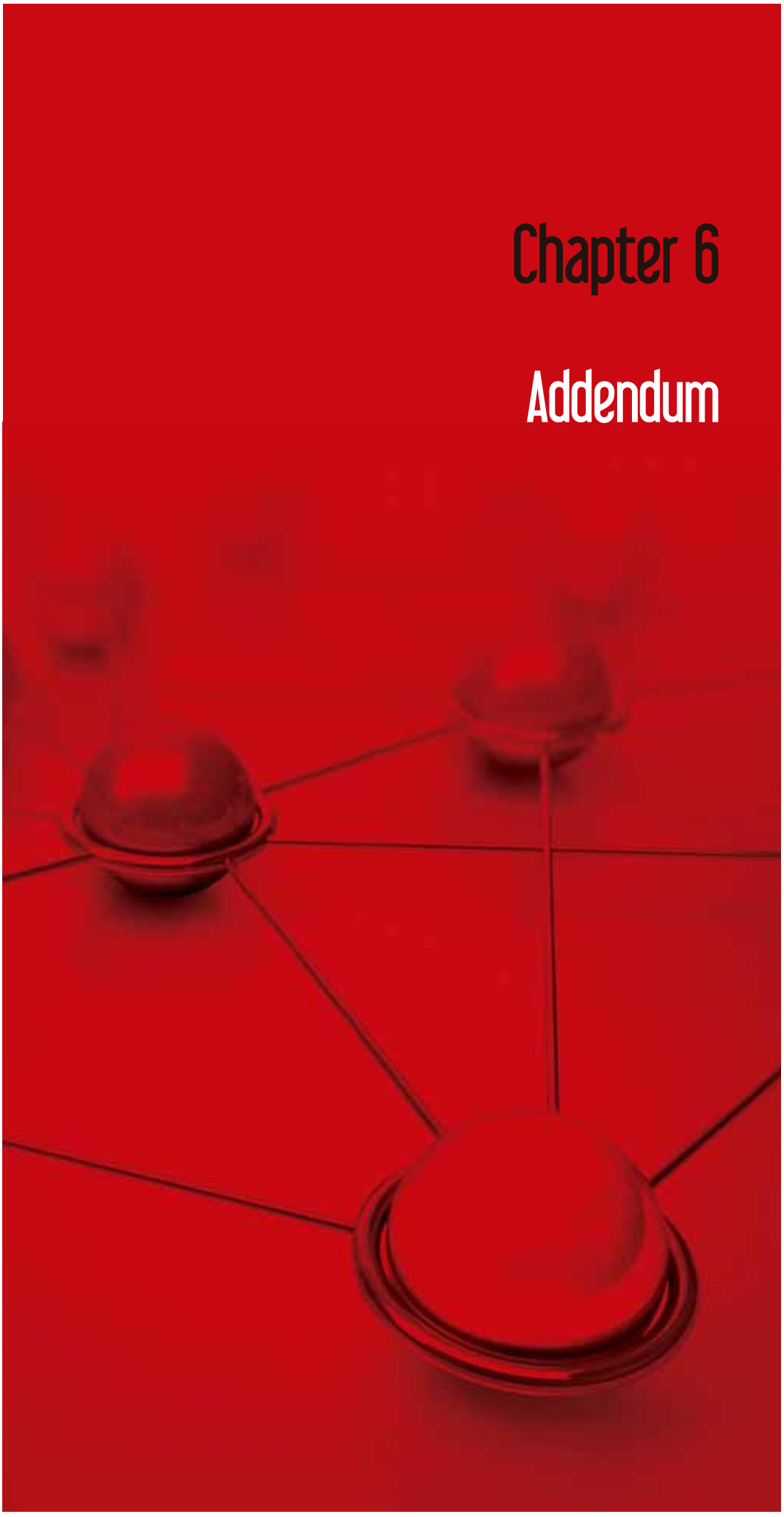
Zoals blijkt uit de onderzoeken beschreven in hoofdstuk 3 van dit proefschrift biedt de bewijskracht uit de dagelijkse praktijk een waardevolle aanvulling op de kennis die vóór toe-

lating tot de markt is opgedaan. Met betrekking tot oudere patiënten zijn kennis over de veiligheid van geneesmiddelen en over het praktische gebruik van geneesmiddelen belangrijk.

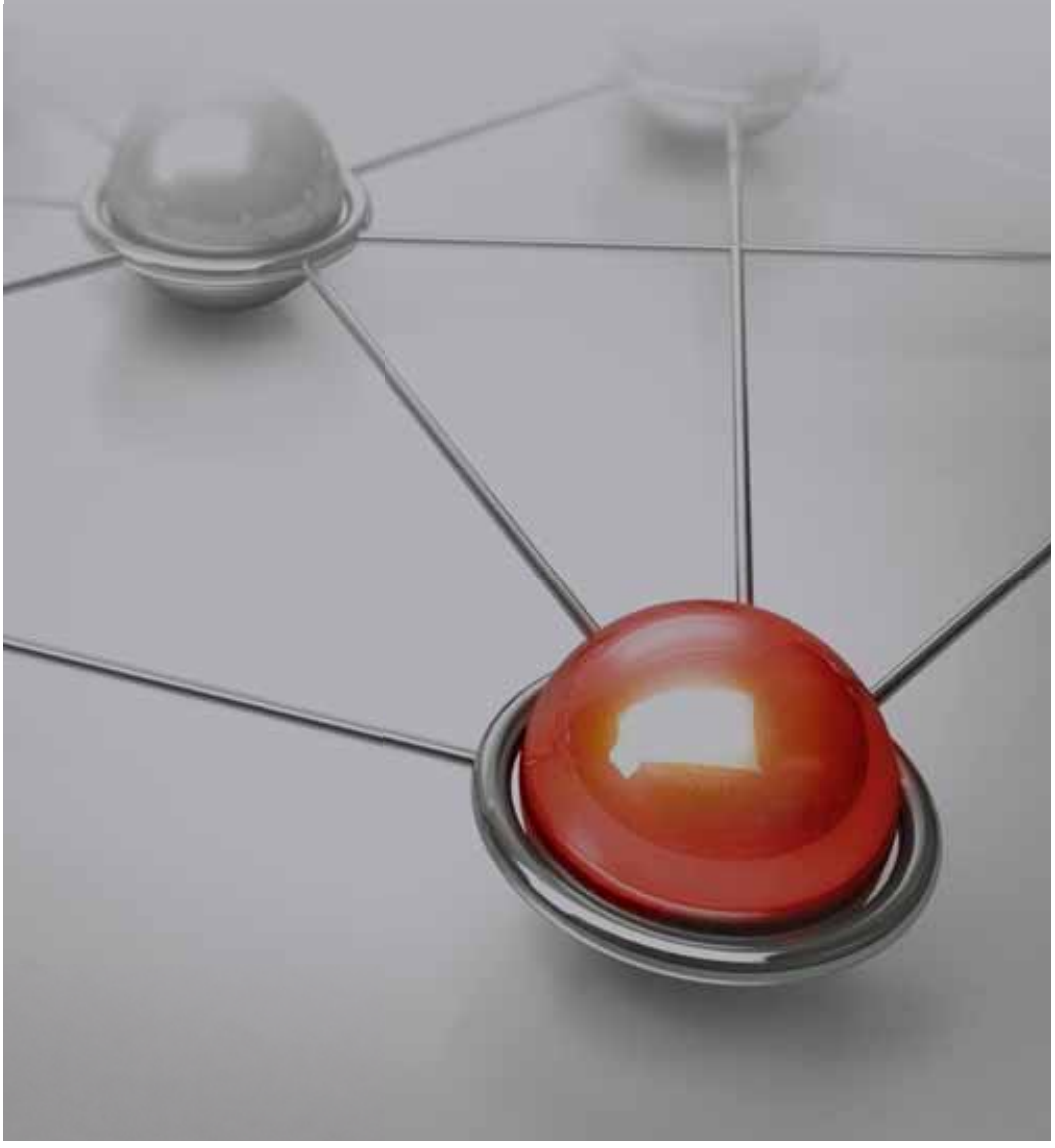
Verbeteringen in de informatie voor het rationeel voorschrijven van geneesmiddelen aan oudere patiënten kunnen alleen dan worden bereikt als alle betrokken partijen hun krachten bundelen.

Chapter 6

Addendum



6.1
Dankwoord



En dan opeens is het moment daar: alles is geschreven, behalve het dankwoord. Hoewel flarden van zinnen al maanden door mijn hoofd spoken, is dit het laatste hoofdstuk dat ik schrijf. En ook nog het enige hoofdstuk dat niet in teamverband tot stand is gekomen. Daarbij is het dankwoord het meest gelezen hoofdstuk van het hele proefschrift. Dat geldt ook voor de stellingen, als die aan een proefschrift toegevoegd zijn. In dit proefschrift ontbreken ze, omdat ze in het Utrechtse geen officieel onderdeel meer vormen van het proefschrift. Toch heb ik in de afgelopen jaren een aantal waardevolle lessen geleerd en uitspraken bewaarheid zien worden. Daarom voeg ik er tien aan dit hoofdstuk toe.

Het is een open deur dat een promotietraject een samenwerkingstraject en een leertraject is. Ik wil iedereen hartelijk bedanken die aan dit proefschrift heeft bijgedragen, direct of indirect.

Allereerst mijn promotoren Prof. dr. Toine Egberts en Prof. dr. Bert Leufkens en mijn copromotor dr. Paul Jansen.

Beste Toine, jou leerde ik kennen in de ziekenhuisapotheek, toen ik als arts vanuit Lareb daar mijn werkkamer had. In die tijd ben ik je kennis, je toewijding en je oog voor bijzondere dingen (zoals paarsgekleurd spuug als bijwerking van omeprazol bij een zuigeling) enorm gaan waarderen. Toen ik vroeg of je mijn promotor wilde worden, gaf je aan dat tijd, kennis van het onderwerp en een prettige band met de promovendus voor jou de redenen zijn om al dan niet promotor te worden. Ik vond het dan ook een compliment dat je mij wilde begeleiden. Dat begeleiden, coachen, heb je met verve gedaan. Je vermogen om, terwijl de rest aan het praten was, een artikel tot op het bot te analyseren en in een paar kernzinnen aan te geven wat er nog moest gebeuren, vind ik nog steeds bewonderenswaardig. Je eenwoords-mailtjes ("ok","ja","doen", maar vooral "erna") schepten nog wel eens verwarring, maar leidden vooral tot hilariteit op de onderzoekerskamer. Een andere doordenker leerde ik van jou toen je mailde: "De drie -raties van onderzoek horen erbij." Na lang nadenken, rondvragen onder je andere promovendi en uiteindelijk jou toch maar mailen, was ik twee dagen later een stelling rijker: Inspi-ratie, transpi-ratie en frust-ratie horen bij onderzoek doen. Ik heb ze alle drie aan den lijve ondervonden. Toch heeft de inspiratie de boventoon gevoerd, mede dankzij jou.

Beste Bert, hoewel ik je wel eens op de jouw kenmerkende bevlogen manier had horen spreken, leerde ik je pas tijdens mijn promotietraject beter kennen. Jouw ideeën zijn onuitputtelijk, je pragmatische oplossingen eveneens. Zo bleek het inderdaad fijn om 'alvast' een gepubliceerd artikel in mijn proefschrift te hebben. Veel andere promovendi roemen je helikopterview, en die kan ik alleen maar onderschrijven. Maar ook heb ik je leren kennen als een netwerker in hart en nieren, zowel tijdens de ICPE in Chicago als tijdens de barbecues in je achtertuin. Dank voor de overheerlijke maaltijden. Je bent een ster in oneliners, waarvan ik er een vooral heb onthouden: Als je het aan de keukentafel niet kunt uitleggen, dan klopt het niet. Ik draag die uitspraak met me mee.

Beste Paul, wij leerden elkaar kennen in 2008. Na een aantal gesprekken over de opleiding tot klinisch farmacoloog vroeg je me of ik promotieonderzoek wilde gaan doen. Het duurde nog

anderhalf jaar voor de subsidie rond was, maar het was het wachten waard. Ik wil je bedanken voor het bieden van de mogelijkheid om mijn beide wensen te vervullen: klinisch farmacoloog worden en vier jaar lang onderzoek doen. In deze periode was je betrokken en altijd snel met het leveren van feedback. Ook kon ik, indien nodig, bij je terecht. Je gaf mij de 'academische vrijheid' om zelf mijn tijd in te delen en thuis te werken, wat erg fijn is als je onderzoek doen combineert met een gezin. Jouw grootste hobby is koken en de les die jij me leerde heeft daar dan ook mee te maken: Waar geneeskunde het recept uit een kookboek volgt, is geneeskunst het bewust afwijken van dat recept. In de geriatrie is dat maar al te vaak nodig, al was het maar omdat de 'kookboeken' zijn geschreven op basis van jongere volwassenen, zoals wel blijkt uit dit proefschrift.

Toine, Bert en Paul, er is een Chinees spreekwoord dat mij aan jullie doet denken: Leraren openen de deur, maar je moet zelf naar binnengaan. Heel veel dank dat jullie deuren voor mij hebben geopend.

De leden van de beoordelingscommissie, prof. dr. J.M.W. Hazes, prof. dr. Y.A. Hekster, prof. dr. M. Petrovic, prof. dr. J.A.M. Raaijmakers en prof. dr. N.J. de Wit, wil ik hartelijk bedanken voor het beoordelen van mijn manuscript.

Ik bracht veelvuldig mijn dagen door op mijn werkkamer thuis, een ongekende luxe als je veel moet lezen, denken en schrijven. Maar het samenwerken tijdens de verschillende onderzoeken was een prettige afwisseling. Ik wil graag alle collega's bedanken met wie ik heb samengewerkt.

Natuurlijk een woord van dank aan mijn paranimfen, Clara Drenth-van Maanen en Ingeborg Wilting. Lieve Clara, jou leerde ik kennen tijdens je stage bij de geriatrie. Ik dacht met je mee bij het onderzoek dat je deed. We waren zelfs samen coauteur bij twee publicaties. Toen wisten we nog niet dat we later collega's en zelfs vriendinnen zouden worden. Het samen onderzoek doen, en het samen doorstaan – maar ook genieten – van de drie –raties, we hebben het allemaal gedaan. Ook aten we regelmatig een taartje, om iets te vieren of om onszelf te beuren, of om welke andere zelfverzonnen reden dan ook. We genoten daar allebei van aangezien we intuïtief wisten wat François de la Rochefoucauld zo mooi verwoordt: Het geluk ligt in de smaak en niet in de dingen zelf. Dat ik een jaar zonder je heb moeten werken, nu je op de interne aan de slag bent, heeft de laatste periode 'significant' minder leuk gemaakt. Je relativeringsvermogen en je bijna stoïcijnse doorzettingsvermogen zijn inspirerend voor me geweest.

Lieve Ingeborg, tja, ik kan nu wel die ene stelling van jou overnemen, maar een onjuiste stelling wil ik toch liever niet in mijn proefschrift plaatsen (je weet vast welke ik bedoel). Mijn eigenwijsheid heeft jouw leven flink op de kop gezet. Gelukkig in positieve zin! Dat alleen al is een reden om jou als paranimf onlosmakelijk met míjn leven verbonden te laten zijn. En dan neem je die taak ook nog heel voortvarend en zo enthousiast op (wat doe je trouwens niet enthousiast?), dat ik daar ontzettend van geniet.

Lieve Clara en Ingeborg, ik vind het een eer dat jullie mij in de laatste fase en op 14 april willen bijstaan op een van de meest bijzondere momenten in mijn leven!

Dan 'mijn' studenten, Dineke, Jeltje en Celestine. Dineke, ik heb het al vaak gezegd: aan jouw gestructureerdheid kan niemand tippen. Ik heb daar heel veel plezier van gehad en ook veel van kunnen leren. Ik vind het fantastisch dat je bent aangenomen voor de opleiding tot klinisch geriater en ik ben ervan overtuigd dat je een fantastisch geriater wordt.

Jeltje, jij was het langst betrokken bij mijn onderzoek, meer dan een half jaar maar liefst. Je hebt een enorme kluif gehad aan het nazoeken van de informatie over 19 onderwerpen (onderverdeeld in 31 items) over 35 geneesmiddelen in 5 internationale handboeken. Je hebt daarmee heel waardevol werk verricht. Ik vond het leuk om te zien dat je je volledig richt op je werk en dat je koste wat kost dingen onder de knie wilde krijgen. Inmiddels ben je bijna dokter. Heel veel succes met je verdere carrière!

Celestine, jij viel me meteen al op door je voorbereiding op ons kennismakingsgesprek. Je had je echt verdiept in het onderwerp en in de onderzoeksopzet. Tijdens je stage maakte je je de statistiek snel eigen en prepareerde je de database heel goed voor de analyses van het enorme CPRD-cohort. Zoals je weet, vond ik het een eer om je als eerste te kunnen feliciteren met je artsenbul tijdens een korte toespraak. Je bent net begonnen aan je eerste baan als anios geriatrie. Heel veel succes.

Dineke, Jeltje en Celestine, ik vond het ontzettend leuk om jullie te begeleiden en om onze kennis te delen. George Bernard Shaw verwoordde dat heel mooi: If you have an apple and I have an apple and we exchange these apples then you and I will still each have one apple. But if you have an idea and I have an idea and we exchange these ideas, then each of us will have two ideas.

Tijdens IMPROVE heb ik vele, vele uren samengewerkt met Kim Notenboom. We bezochten samen geriatrisch patiënten om ze te interviewen, we analyseerden de uitgewerkte interviews, stelden de coderingen op en zo nog meer. Ik heb geleerd dat paracetamol best met kokend water overgoten kan worden, dat een restje van een dispergeerbare tablet geen actieve stof meer bevat en dat er 'snaptabs' bestaan. We hebben veel lol gehad, zeker na het doornemen van weer eens honderden pagina's tekst. Hoewel de volgende uitspraak een stelling zou kunnen worden, ben ik er nog niet over uit of die lang geciteerd zou gaan worden: Bas taste is bad tatse? Kim, dank voor de samenwerking en veel succes met jouw promotietraject!

Dr. Patrick Souverein, je initialen zijn 'pc' en je ouders hadden die niet beter kunnen kiezen. Met je laptops, desktops en harde schijven op je bureau kon je de enorme CPRD-database 'kraken'. Je snelheid (sneller dan het draaien van de analyses) is bewonderenswaardig. Je gezelligheid zal ik niet vergeten. Dank voor je hulp!

Prof. dr. Tjeerd van Staa, jouw enorme farmacoepidemiologische kennis heeft de CPRD-studie de vorm gegeven die het nu heeft. Je rust en je heldere uitleg zijn van onschatbare waarde. Dank daarvoor!

Dr. Imke Bartelink, ver weg in de VS, dank voor je enthousiaste bijdrage aan het valproaat-artikel en onze gezellige diners.

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Prof. dr. Marcel Bouvy, als praktiserend openbaar apotheker met grote betrokkenheid bij oudere patiënten tijdens IMPROVE vond ik je opmerkingen en aanvullingen heel waardevol.

Drs. Diana van Riet-Nales, dank voor je altijd snelle en uitgebreide feedback op het manuscript van IMPROVE en voor het delen van jouw kennis over de Paediatric Regulation. En veel succes met jouw laatste promotieloodjes.

Naast de bovengenoemde coauteurs hebben veel mensen op de achtergrond een belangrijke rol gespeeld.

José de Vries, stafsecretaresse, dank je wel voor het altijd paraat staan, voor het regelen, verzetten en opnieuw verzetten van afspraken, voor heel veel ander regelwerk, en voor de vele gezellige momenten. Paars, groen en roze bleken ons allebei toch het beste te passen.

Ineke Dinzey, Anja Elbertse en Suzanne de Visser, de secretaresses van de 'overkant', ook jullie hadden de uitdagende taak om afspraken te plannen in de agenda's van de drukbezette mannen. Dank voor de ondersteuning in de afgelopen jaren.

Drs. Svetlana Belitser, je hebt je hoofd gebroken over de analyse van de enquêtes. Dankzij jouw inzicht en razendsnelle analyses in R konden we het onderzoek op een gedegen manier afronden en publiceren in een mooi tijdschrift. Dank je wel!

Jane Sykes, vrijwel alle Engelstalige hoofdstukken uit dit proefschrift heb je gecorrigeerd. Met jouw kennis van zaken werden de teksten altijd nog mooier. Heel veel dank voor al je leerzame feedback!

Frank Boesveld, voor een aantal hoofdstukken maakte jij de figuren, zoals die mooie in de general introduction. Om tot een goede visuele weergave van de wetenschappelijke cijfers te komen dachten we samen na, wat ik ervoer als een prettige synergie. Dank je wel!

Tijdens IMPROVE was de hulp achter de schermen het grootst. Ria Frijters, Mandy Jedeloo, Marry Osnabrugge en Betty Vuyk, secretaresses van de afdeling geriatrie in het UMC Utrecht, maar ook farmaciestudenten Corine Bethlehem en Hanneke Luttikhuis hebben uren besteed aan het transcriberen van de interviews: één uur typen per tien minuten

interview. Dank daarvoor! Het leeuwendeel daarvan deed Marianne Versloot, naast het mee uitvoeren van het onderzoek. Beste Marianne, jou wil ik ook bedanken. Ik vond het kletsen (en dat konden we!) in de auto van en naar de interviews erg gezellig. We genoten van de zelfgebakken appeltaart van een deelnemer en van de soms bijzondere situaties en mooie verhalen die we hoorden. Je hebt me ook fantastisch geholpen bij het completeren van het studiedossier. En ja, ik parkeer nog steeds het liefst op de beste plek in de parkeergarage. Dank voor al je hulp en je gezelligheid!

Dat dit proefschrift er zo prachtig uitziet, heb ik ook te danken aan een team. Charles Dumas, directeur van Prelum Uitgevers, dank je wel dat jij het idee opperde. Gina Doedens, uitgever van Psyfar, jij werkte het tot in de puntjes uit. En dat niet alleen: je zorgde ook nog voor uitgebreid advies over de Werkelijk Belangrijke Zaken. Beste Gina, dank je wel voor alles, niet in de laatste plaats voor de gezellige besprekingen in Laren, die steevast te lang duurden. Anouk Kwantes, vormgever bij CO_2 Premedia, jij gaf het proefschrift letterlijk en figuurlijk vorm. Dat ging prettig en vlot. Ontzettend veel dank voor dit prachtige werk! Jenny Sweben, redactiecoördinator bij Prelum, jij liet de gang naar de drukker soepel verlopen. Dat gaf heel veel rust in de laatste periode. Ook jij heel erg bedankt! Op de laatste pagina van dit proefschrift staat een foto die niet mooier had kunnen zijn. Job Jonathan Schlingemann, dank je wel voor het kunstwerk.

Voor praktische, methodologische, maar vooral mentale ondersteuning tijdens het doen van onderzoek, dus bij inspiratie, maar ook bij frustratie, zijn kamergenoten van onschatbare waarde. Naast Clara Drenth-van Maanen, was dat in de beginperiode Frederiek van den Bos. Lieve Frederiek, we hebben tijdens mijn eerste jaar een heel gezellige tijd gehad, waarbij jij als een doorgewinterde coach fungeerde. In de jaren daarna, toen jij naar het Haagse was vertrokken, waren de ontmoetingen tijdens de congressen in Malaga en Venetië, maar ook vorig jaar als collega-paranimf, altijd warm, vrolijk en gezellig. Ook met Karen Keijsers deelden we de kamer. Beste Karen, jij bent de derde van 'Paul's Angels' die gaat promoveren. Je bevlogenheid, in goede en minder goede tijden, straalt altijd van je af. Zet 'm op tijdens de laatste loodjes. Joyce de Wit, je gedrevenheid en enthousiasme in je werk maar ook in je toneelspel werken aanstekelijk. Ik wens je een mooie toekomst, hoe die er ook uit zal zien. Kim Blom, jij barst van de energie en de humor. Als ik onze kamer opkom, mis ik je meteen als je er niet bent. Zet 'm op met je onderzoek, je coschappen, wat daarna allemaal gaat komen, en natuurlijk met de muziek en de andere veelbesproken zaken.

Naast een team van collega's en kamergenoten, zijn vrienden en buiten het werk en familie heel belangrijk. Om te reflecteren op het werk, de onderzoeken, maar zeker ook om het werk even te vergeten.

Eugène van Puijenbroek, hoewel je natuurlijk ook coauteur was, noem ik je hier, omdat je meer nog dan een ex-collega een vriend bent geworden in de afgelopen jaren. Toen ik je vroeg of promoveren wel te combineren zou zijn met een gezin, zei je volmondig 'ja'. Dat gaf mij het

vertrouwen de stap te zetten. Dank je wel voor het zetje in de goede richting. Je weet dat ik onze vrijdagmiddaghumor mis. Nog krijg ik spontaan de slappe lach als ik denk aan de *organ player* of de ballon in het hondje van je tante. Ik hoop dat we nog heel lang de dinertjes in Woerden kunnen voortzetten. Dank voor al je steun en gezelligheid!

In één adem met Eugène noem ik natuurlijk Annemarie Bijl. Je enthousiasme en je steun zijn opbeurend. Ik weet niet eens of je het nog weet, maar van jou heb ik een bijzondere stelling geleerd, die meer dan een stelling inmiddels een lijfspreuk is geworden: "Vooruit is niet altijd rechtdoor." Dank je wel voor die wijsheid!

Bij deze twee vrienden hoort natuurlijk Jerry Labadie. Hoe graag zou ik je bij deze dag hebben gehad. Je foto staat bij mijn bureau, omdat je een inspiratiebron was, bent en blijft. Ik wou dat ik het je vaker had kunnen zeggen: dank je wel daarvoor.

Lieve Jelma, onze meiden werden dikke vriendinnen, en wij al heel snel ook. Ondanks de zorg voor je drie kinderen en je drukke baan, heb je altijd oog voor wat er in andermans leven gebeurt. Een bijzonder mooie eigenschap! We hebben heel wat uren thee gedronken op onze woensdagochtenden. De laatste maanden is dat er bij ingeschoten, omdat bij ons allebei het werk doorsijpelde in onze vrije tijd. Daarnaast heb je, als neerlandica en doorgewinterde papierverslinder, meegelezen in de laatste fase van mijn onderzoek, toen de druk hoog en de termijnen kort waren. Ik waardeer het enorm dat je daarvoor tijd wilde vrijmaken. Dank voor alles!

Lieve Petra, ook wij zijn als 'moeder van' begonnen toen onze meiden vriendinnen werden, maar we delen inmiddels lief en leed en zien elkaar minstens drie keer per week. Jouw opgewektheid, creatieve geest (kleuters laten 'toveren' met een mix van water, paprikapoeder en bakpoeder), maar ook je snelle analytische blik èn je eerlijkheid maken dat ik jou en onze vriendschap enorm waardeer. Bovendien weet jij wanneer het tijd is voor een feestje: hoewel het bedtijd was, stond de prosecco voor me klaar toen ik je wapte dat mijn proefschrift klaar was. Dank je wel voor je vriendschap!

Heit en mem, jullie stonden aan de wieg van een wetenschapper in de dop. Het vragen naar het 'waarom' heb ik in de afgelopen jaren tot in de finesses kunnen uitwerken. Het schrijven, maar ook het onderwijzen heb ik in mijn genen meegekregen. Het geeft me de energie die ik herken van heit, als hij les gaf. Ik ben jullie dankbaar dat jullie me de kans hebben gegeven me te ontplooien in de richtingen die ik wilde. Aristoteles zei al: Opleiding is de beste proviand op de reis naar de ouderdom. Dank jullie wel!

Lieve Martijn, wat ben ik blij met jou. Van het citaat: A (wo)man who wants time to read and write must let the grass grow long, van Sloan Wilson, heb jij de gevolgen maar al te vaak ondervonden. Vooral in de laatste tijd, waarin jij vrijwel alles draaiende hield. Ik wil je bedanken voor je praktische steun, maar ook je luisterend oor, je kritische blik, je zorgzaamheid, je liefde en je geduld in de afgelopen jaren. Wat mij betreft kopen we kunstgras en gaan we genieten van de komende tijd!

Lieve Anna, je bent de laatste die ik noem in dit proefschrift. Maar ook de eerste, want dit proefschrift draag ik op aan jou, omdat ik je graag wil meegeven dat je gelukkig wordt van dingen waar je energie van krijgt. Voor mij was dat het doen van dit onderzoek, het leren, het lesgeven en het bijwonen van congressen. Dat betekende dat je me geregeld moest missen, vooral in de laatste maanden. Dat vonden we allebei niet altijd leuk. Nu hebben we gelukkig weer de tijd. Ik hoop dat je onthoudt, voor nu en voor later, dat als je dingen doet waar je energie van krijgt, je die energie kunt delen met degenen van wie je houdt.

6.2
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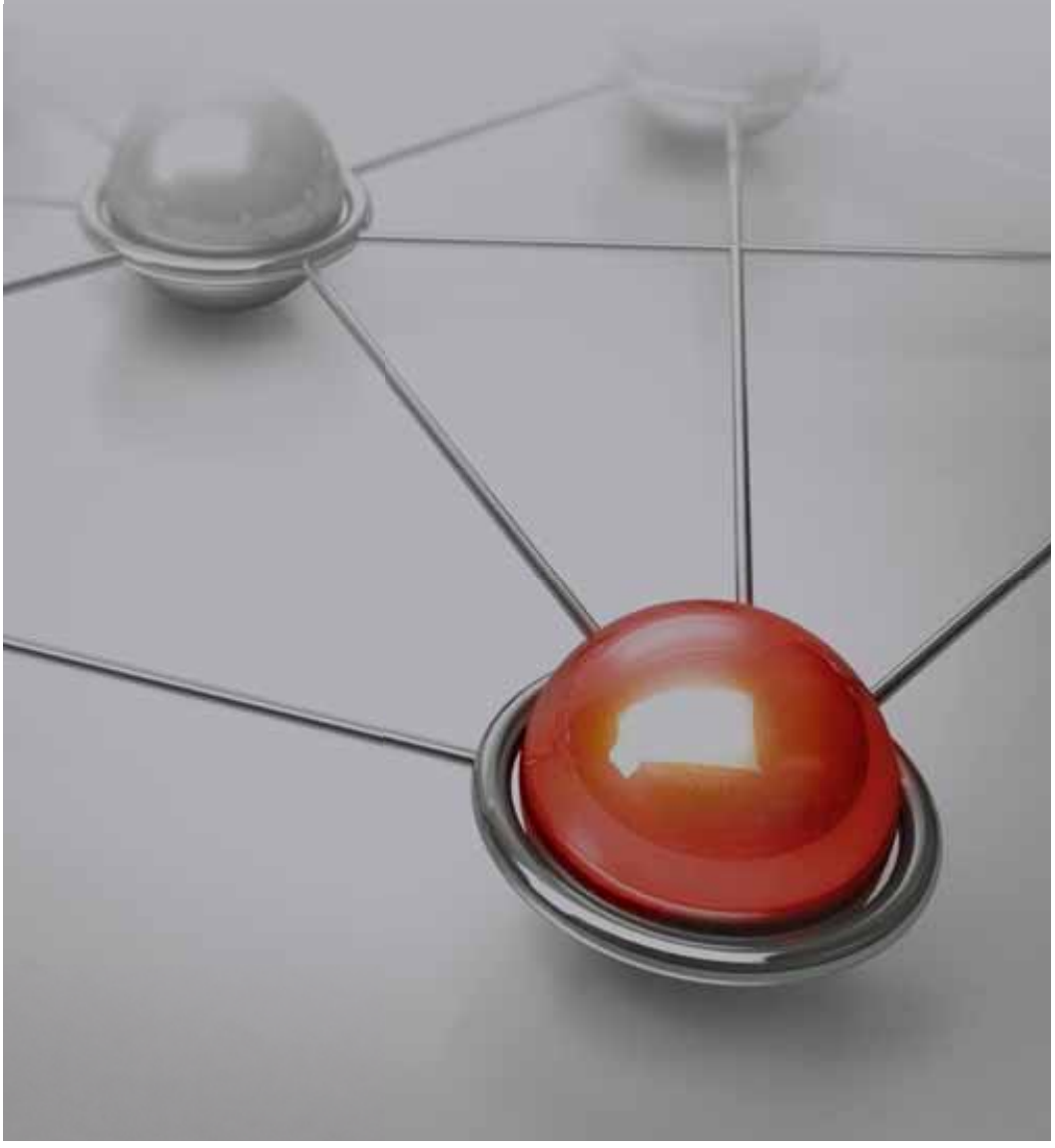

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6.3
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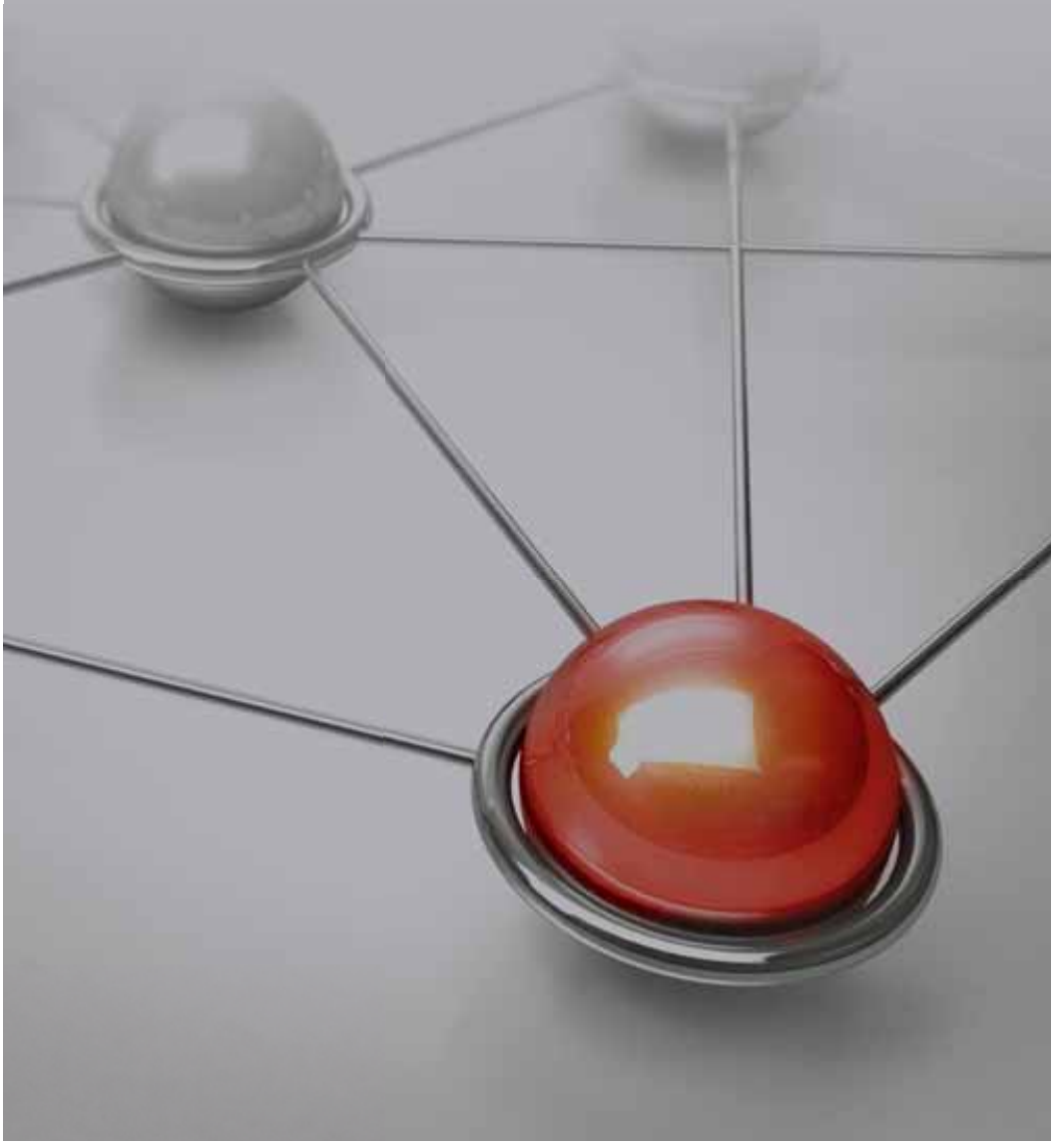

Publications related to the subject of this thesis

Beers E, Egberts TC, Leufkens HG, Jansen PA. The views of healthcare professionals, drug developers and regulators on information about older people needed for rational drug prescription. *PLoS One* 2013;8:e72060.

Beers E, Egberts ACG, Leufkens HGM, Jansen PAF. Informatie over ouderen in het Farmacotherapeutisch Kompas en de officiële productinformatie van antipsychotica. *Ins & Ouds* 2013;1:5-8.

Beers E, Egberts TCG, Leufkens HGM, Jansen PAF. Information for adequate prescribing to older patients: An evaluation of the product information of 53 recently approved medicines. *Drugs Aging* 2013;30:255-62.

Beers E, Egberts TCG, Leufkens HGM, Jansen PAF. Voorschrijven van antipsychotica; wat staat er in Kompas en productinformatie? T*ijdschrift voor Ouderengeneeskunde* 2012;3:127-31.

Beers E, van Puijenbroek EP, Bartelink IH, van der Linden CM, Jansen PA. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatraemia associated with valproic acid: Four case reports from the Netherlands and a case/non-case analysis of Vigibase. *Drug Saf* 2010;33:47-55.

Jansen PAF, van Maanen AC, van Marum RJ, van der Linden CMJ, Beers E, Egberts ACG. Vermijdbare bijwerkingen – Individuele electronische pharmacovigilantie biedt uitkomst. *Medisch Contact* 2007; 62:637-40.

Jansen PAF, van Maanen AC, van Marum RJ, van der Linden CMJ, Beers E, Egberts ACG. Vermijdbare bijwerkingen. Systeem voor individuele Electronische Pharmacovigilantie biedt uitkomst. *Pharm Weekbl* 2007;142:32-4.

Beers E, de Groot MCH. Anticholinerge bijwerkingen van geneesmiddelen bij ouderen. *Pharm Weekbl* 2006;141:988-9.

Scientific publications not related to the subject of this thesis

Galyuk TM, de Backer G, de Jong CA, Beers E, Loonen AJ. Misbruik van quetiapine. Twee verslaafde patiënten met een borderlinepersoonlijkheidsstoornis. *Ned Tijdschr Geneeskd* 2009;153:674-6.

Van Marum RJ, Wegewijs MA, Loonen AJ, Beers E. Hypothermia following antipsychotic drug use. *Eur J Clin Pharmacol* 2007;63:627-31.

Beers E, van Grootheest AC. Bruxisme als bijwerking van serotonineheropnameremmers. *Ned Tijdschr Tandheelkd* 2007;114:388-90.

Beers E, Loonen AJ, Van Grootheest AC. Suïcidale ideaties en suïcidepogingen na instelling op aripiprazol, een nieuw antipsychoticum. *Ned Tijdschr Geneeskd* 2006;150:401-2.

6.4

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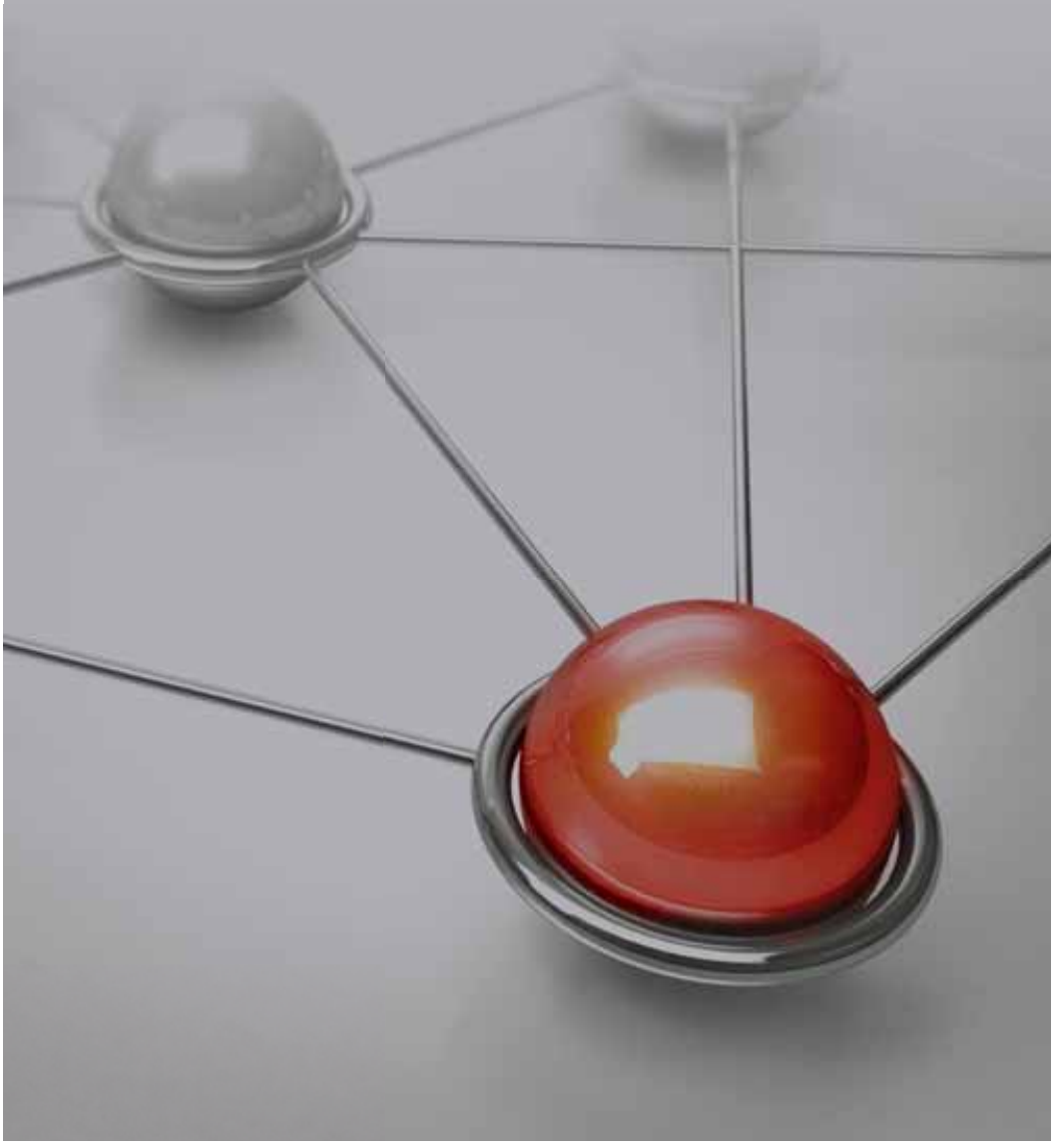

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