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Adverse Consequences of Drug Use in the Elderly

Ongewenste effecten van geneesmiddelengebruik bij ouderen

Proefschrift

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1

General introduction

Although drug therapy often results in beneficial effects and improves functional status, adverse consequences of pharmacotherapy are a major patient safety concern, especially in the growing older population [1]. In the well-known report 'To err is human: building a safer health care system' [2], it was brought forward that a substantial number of patients is harmed by adverse drug events in medical care. This report placed patient safety and drug safety on the international agenda and was the basis for many policy and health care initiatives to make health care safer.

Apart from the vulnerability of a patient to develop an adverse drug reaction, drug safety has several aspects, among which are deficient product quality, quality of prescribing and administration, and patient compliance. In this thesis, we focus on the quality of prescribing and on adverse consequences of pharmacotherapy in the elderly, because in the aging western countries this is a vulnerable patient group of increasing importance. In view of multiple co-morbidity, changes in pharmacokinetics and pharmacodynamics and concomitant use of several drugs simultaneously (polypharmacy), elderly people are at increased risk of drug-related problems [3]. Moreover, several studies on drug utilisation and quality of prescribing in elderly patients have demonstrated high levels of drug use and a considerable number of patients receiving inappropriate medications [4,5]. Inappropriate medication use for older adults can be defined as medication use for which the potential harm outweighs the potential benefit and for which a good alternative is available [6]. This alternative could be the prescribing of an other (safer) drug or prescribing a drug in a lower (geriatric) dose, in order to decrease the risk of adverse drug events in this vulnerable group.

Drug use can lead to serious adverse consequences such as major adverse effects (e.g. allergic reactions, intoxications), or even to hospitalisations or death. Some adverse drug effects are not preventable, such as type B (idiosyncratic) reactions, which are almost always unpredictable. However, most adverse drug effects are type A (pharmacological) reactions and may be preventable [7]. These reactions can be predicted from the known pharmacology of the drug and are dose-dependent. Pharmacological adverse drug reactions include events due to drug-drug interactions, use of contra-indicated drugs or prescribed daily doses that are too high for certain patients.

Elderly people are usually not included in randomised clinical trials, both because of unfavourable pharmacokinetic or –dynamic characteristics and co-morbidity [8]. As a result information on efficacy, optimum drug dosages and toxicity are frequently lacking in this group [9-11]. Therefore, prescribers regularly lack a thorough understanding of the risks, benefits and consequences of drug therapy in the elderly. Studying drug use and drug effects in this group in daily clinical practice can give more insight into these matters and provide tools for appropriate

prescribing. Adequate drug prescribing by taking into account the benefits and risks of certain drugs in an older patient is of major clinical importance and may prevent a significant burden of adverse events and health care costs.

Objective and outline of the thesis

The objective of this thesis was to investigate the extent of inappropriate drug prescribing in the Netherlands and to study clinically important adverse consequences of (inappropriate) drug use in the elderly population. For this goal, we used 2 population-based data sources: 1) the Rotterdam Study, a prospective population-based cohort study among 7983 older adults living in Ommoord, a suburb of Rotterdam [12] and 2) the Integrated Primary Care Information (IPCI) project, a general practice research database with all computer-based patient records from a group of 150 general practitioners in the Netherlands, covering more than 500.000 patients [13,14]. Additionally, we were able to use the 'Landelijke Medische Registratie' (LMR) database, a registry that stores discharge information from all hospitalisations in the Netherlands.

In chapter 2, we first describe the extent of potentially inappropriate drug prescribing in the Netherlands, based on the internationally known Beers criteria, which were recently updated [15] (chapter 2.1). Second, we assess the consequences of inappropriate drug use based on these criteria by studying the association between wrong use of benzodiazepines and the risk of fractures (chapter 2.2). In chapter 3, we investigate the extent of hospitalisations due to adverse drug reactions (ADRs) and its determinants. First, we study the proportion of ADR-related hospitalisations in the Netherlands based on the LMR (chapter 3.1) and in the second study, we assess ADR-related hospitalisations based on hospital discharge letter review and general practitioner information from the IPCI database (chapter 3.2). In Chapter 4, we focus on atrial fibrillation, an arrhythmia with a high occurrence in the elderly population. This arrhythmia can be induced by drugs. We review which drugs have been associated with atrial fibrillation in the literature, since little is known about drug-induced atrial fibrillation (chapter 4.1). Subsequently, we investigate the association between corticosteroid use and the risk of atrial fibrillation in an epidemiological study, because there is hardly anything known about this association (chapter 4.2). In chapter 5, we reflect on our main findings and discuss several methodological issues related to the topic of this thesis, and speculate on the implications of our results.

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2

Prevalence and consequences of inappropriate drug use in the elderly

2.1

Potentially inappropriate drug prescribing in older adults: the 2002 Beers criteria

Abstract

Background: In 1997, Beers et al. developed explicit criteria for potentially inappropriate drug prescribing in ambulatory older adults aged 65 years and over. Several studies have been performed to estimate the prevalence of inappropriate drug prescribing based on these criteria. In 2002, the criteria were updated.
Objective: To examine the extent and trend of inappropriate drug prescribing to ambulatory older adults in the Netherlands between 1997 and 2001, according to the 1997 and the updated Beers criteria.
Methods: Data were retrieved from the Integrated Primary Care Information (IPCI) project, a general practice research database with data from computer-based patient records of a group of 150 general practitioners in the Netherlands. All subjects aged 65 and over were included. Prescriptions were classified as inappropriate if they fulfilled the Beers criteria of prescriptions that generally should be avoided in older adults because of a high risk of adverse effects, while also considering dose and co-morbidity.
Results: Between 1997 and 2001, the one-year risk of receiving at least one inappropriate drug prescription for older adults ranged between 16.8% (95% CI: 16.3%-17.3%) and 18.5% (18.3%-18.7%) according to the 1997 criteria and between 19.1% (18.6%-19.6%) and 20.0% (19.5%-20.5%) according to the updated Beers criteria. According to the updated criteria, the most frequently prescribed inappropriate drugs were nitrofurantoin, long-acting benzodiazepines, amitriptyline, promethazine and cimetidine. Temazepam and zolpidem were mostly prescribed in supratherapeutic dose. Conventional NSAIDs in persons with a history of gastric/duodenal ulcer were the most frequently prescribed contra-indicated drugs.
Conclusions: Prescribing potentially inappropriate prescriptions to ambulatory older people in the Netherlands is substantial. Compared to other studies using the 1997 Beers criteria, inappropriate prescribing to the elderly is lower than in the USA but similar to Finland. Despite a restrictive medication policy and a growing attention for medication surveillance in Europe, inappropriate drug prescribing is still a substantial problem.

Introduction

Inappropriate medication use is a major patient safety concern, especially for the growing older population. Polypharmacy and use of inappropriate drugs in this group increase the risk of adverse drug reactions [1]. Inappropriate medications for older adults are defined as medications for which the potential risk outweighs the potential benefit and for which a good alternative drug is available [2].

In 1997 Beers and colleagues developed a comprehensive set of explicit criteria for potentially inappropriate drug use in ambulatory elderly aged 65 years and over. These criteria were developed with the intention of providing a useful tool for assessing the quality of prescribing in older persons, regardless of their level of frailty or their place of residence [2]. Drugs were classified as inappropriate in three categories: 1) drugs that generally should be avoided in older adults, 2) drugs that exceed a maximum recommended daily dose and 3) drugs to be avoided in combination with specific co-morbidity. Although for individual cases the listed drugs may be appropriate, the set of criteria may be used in drug utilization reviews, as the basis for educational materials and for assessing the quality of prescribing [3]. Recently, Beers et al. presented the results of updating the 1997 criteria which was done by a panel of experts in the USA [4], now called the 2002 criteria.

Previous studies using the Beers criteria were limited to the first category, i.e., drugs that generally should be avoided in older adults (general list). Studies in the USA estimated that between 17.5 % and 23.5 % of the ambulatory elderly population use at least one inappropriate drug from the general list [1,5-7]. A population-based survey in Finland estimated a prevalence of 12.5 % [8], also based on the general list of the 1997 criteria. The other two categories (considering dose and co-morbidity) have never been properly evaluated in an older population.

In the updated Beers criteria (2002 criteria), changes mainly involve new medications which were added to the general list, but also several drugs were removed and there was a modification of the co-morbidity list. To our knowledge, no studies have been performed yet with these new criteria and few European data on inappropriate drug use in the elderly are available. Therefore, we performed a population-based cohort study to estimate inappropriate medication prescribing to older adults in the Netherlands based on the updated Beers criteria while considering all three categories of inappropriate use. To compare our results with previous studies and to evaluate the impact of the updated criteria, we also assessed the 1997 Beers criteria.

Methods

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a general practice research database, containing data from computer-based medical patient records of a group of 150 general practitioners (GPs) in the Netherlands. In the Dutch health care system, the GP has a pivotal role by acting as a gatekeeper for all medical care. Details of the database have been described elsewhere [9,10]. Briefly, the database contains the complete medical records of approximately 500,000 patients. The electronic records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses (using the International Classification for Primary Care [11] and free text) from GPs and specialists, referrals, laboratory findings, hospitalisations, and drug prescriptions. The drug prescription records include the following information: brand & generic name, indication, dosage regimen and Anatomical Therapeutic and Chemical (ATC) codes [12]. To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain paper-based records besides the electronic medical records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research in several studies that evaluated the quality of the available information [10]. The population in this database is representative of the Dutch population regarding age and sex. The Scientific and Ethical Advisory Board of the IPCI project approved this study.

Design, study population and study period

We conducted a population-based cohort study in a dynamic population of older adults aged 65 and over, with at least one year of valid database history. The study period started on January 1, 1997 and ended on December 31, 2001. All subjects in the study population were followed from 1 January 1997, the date of their 65th birthday, or the date of one year of valid history, whichever was latest, until the earliest of one of the following censoring points: death, transferring out of the practice, or end of the study period.

Changes in Beers criteria between 1997 and 2002

Recently, Beers et al. presented the results of updating the 1997 criteria [4]. The initiative to revise and update the 1997 criteria had three main aims: (1) to re-evaluate the 1997 criteria, to include new drugs and incorporate new information available from the scientific literature, (2) to assign or re-evaluate a relative rating of severity for each of the medications and (3) to identify any new conditions or

considerations not addressed in the 1997 criteria [4]. New conditions and diagnoses were added, such as depression, cognitive impairment and Parkinson's disease. A total of 15 medications and medication classes were dropped or modified from the 1997 to the 2002 update. Most of the medications dropped since 1997 were those that were associated with co-morbidity. Medications that were dropped include: phenylbutazone; dipyridamole; beta-blockers in persons with diabetes mellitus, chronic obstructive lung disease (with exception of propranolol), peripheral vascular disease, syncope and falls; and narcotics in persons with bladder outflow obstruction. Oxybutynin was modified by not including the extended-release formula. The update also includes several medications that have new information or have come to the market since the 1997 criteria, including amiodarone, fluoxetine, nitrofurantoin and cimetidine.

Classification of inappropriate drug prescriptions and co-morbidity assessment

Three categories of inappropriate drug prescriptions according to the 1997 and 2002 Beers criteria were generated, namely: 1) drugs that generally should be avoided in older adults because of a high risk of adverse effects, 2) drug prescriptions that exceed a maximum recommended daily dose and 3) drugs to be avoided in combination with certain co-morbidity. Drugs were coded according to the ATC classification system [12]. To assess supra-therapeutic doses according to the Beers criteria, we used the prescribed daily dose which was available in the prescription records. Co-morbidities (diagnoses) were coded according to the International Classification of Primary Care (ICPC) [11]. The prevalence of co-morbidities was obtained by searching on ICPC diagnostic codes and was assessed during or prior to the year of interest. For assessment of an inappropriate drug-comorbidity combination it was required that the disease or condition occurred prior to the prescription of interest. Several of the listed drugs are not marketed in the Netherlands and were therefore excluded from the analysis. These concerned: meperidine, trimethobenzamide, dicyclomine, chlorpropamide, propantheline, carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, chlorpheniramine, hyoscyamine, diphenhydramine, tripelennamine, reserpine, ticlopine, guanethidine, guanadrel, quazepam, halazepam, methyltestosterone, mesoridazine, desiccated thyroid and amphetamine.

Risk assessment

Per calendar year we calculated the one-year risk of receiving at least one inappropriate prescription according to both the 1997 and the 2002 criteria. The one-year risk was calculated as the number of patients aged 65 years and older who received at least one inappropriate prescription divided by the total

number of patients aged 65 years and over present during that whole year. We did this for the three categories separately and combined. Drug specific risks are shown for the most recent study year only. Ninety-five percent confidence intervals around risk estimates were calculated based on the normal distribution.

Results

The study population for each year ranged from 18,030 to 29,605 persons aged 65 years and older over the years 1997 to 2001. The mean age of the study population remained rather stable over the years, namely approximately 74 years. Almost 60% was female and around 85% of the study population received at least one drug prescription per year (**table 1**).

Taking all three Beers categories together (i.e. general list, dose-related list and co-morbidity list), the one-year risks of receiving any inappropriate prescription ranged between 16.8 % (95% CI: 16.3%-17.3%) and 18.5% (18.3-18.7%) over calendartime according to the 1997 criteria and from 19.1% (18.6-19.6%) to 20.0% (19.5-20.5%) according to the 2002 criteria (**figure 1**). The higher risk following the 2002 criteria was caused by an increase in prevalence of inappropriate prescribing from the general list. According to the 1997 criteria, the annual risk of receiving an inappropriate prescription increased from 1997 to 2002. This trend was not observed with 2002 criteria.. For the 'overdose' list (drugs that should not exceed a maximum dose), the annual risk of receiving an inappropriate prescription was the same comparing the old and the new criteria. For the co-morbidity list (drugs to be avoided in combination with certain co-morbidity), the one-year risk of receiving an inappropriate prescription was higher according to the 1997 criteria (risk ranges from 5.9 (5.6-6.2) % to 8.5 (8.2-8.8) %) than according to the 2002 criteria (risk ranges from 4.1 (3.8-4.4) % to 5.1 (4.8-5.4) %). However, both showed a trend of increasing annual risks.

In 2001, the most frequently prescribed inappropriate drugs from the general list were long-acting benzodiazepines, amitriptyline, dipyridamole and promethazine according to the 1997 criteria. Nitrofurantoin, long-acting benzodiazepines, amitriptyline, promethazine and cimetidine were the most frequently prescribed inappropriate drugs according to the 2002 criteria (**table 2**).

The drug most frequently prescribed in a supratherapeutic dose was temazepam (2% of the study population used temazepam and almost 30% of users received a supratherapeutic dose). Of the zolpidem users, 92% received a supratherapeutic dose according to the Beers criteria, but this drug is not prescribed frequently (0.9% of the study population) and the potential adverse effects are minor (**table 3**).

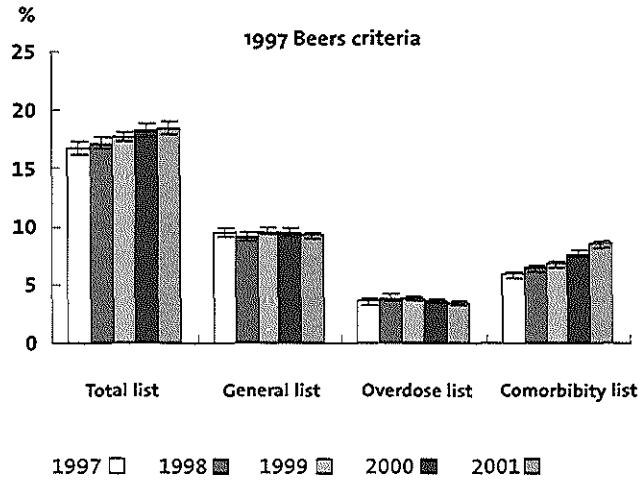
Table 4 shows the prevalence of inappropriate prescribing in relation to co-morbidity. According to the 1997 criteria, the most frequent inappropriate use was that of beta-blockers in diabetes patients (28.7%). Since this criterion was removed in 2002, the most frequent inappropriate use given co-morbidity according to the 2002 criteria was of conventional NSAIDs in persons with a history of gastric/duodenal ulcer (26.6%) and of short-intermediate/long acting benzodiazepines in subjects with (previous) syncope or falls (26.4%). The prevalences were about the same in other years.

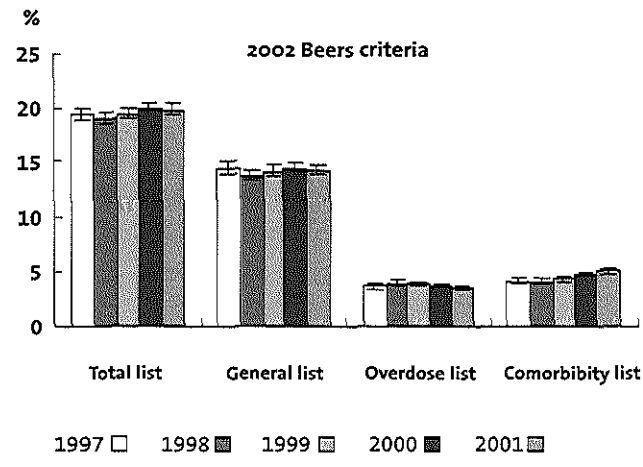
Table 1 Baseline characteristics of the study population in each calendar year

Characteristics	1997 N=18,030	1998 N=20,947	1999 N=29,605	2000 N=26,378	2001 N=25,258
Demographics					
Mean age, y	74.5	74.5	74.7	74.8	74.9
Female sex, %	59.7	59.2	59.1	58.8	58.5
Any drugs prescribed, %	84.9	85.0	85.7	85.8	85.9
Co-morbidity, %					
Heart failure	5.3	5.8	5.5	5.8	5.9
Diabetes mellitus (treated)	8.5	9.3	9.8	10.2	11.0
Hypertension	18.4	18.1	17.6	19.2	20.1
COLD*	5.4	6.1	6.1	6.5	6.6
Gastric/ duodenal ulcer	6.2	6.5	6.5	7.2	7.7

* COLD = chronic obstructive lung disease (asthma/COPD)

Figure 1 Prevalence of inappropriate prescribing in elderly between 1997-2001, according to the 1997 and 2002 Beers criteria, bars represent 95% CI





1997: N=18,030 **1998:** N=20,947 **1999:** N=29,605 **2000:** N=26,378 **2001:** N=25,258

Table 2 Inappropriate drug prescribing from general list in year 2001, N=25,258

Type of medication	Severe potential adverse effects	Criteria 1997	Criteria 2002
Any general inappropriate drug prescribed (list below), % (95% CI)		9.3 (9.0-9.7)	14.3 (13.9-14.7)
Specific drugs, %			
Indomethacin	Yes	0.5	0.5
Pentazocine	Yes	< 0.1	< 0.1
Oxybutynin (immediate release)	Yes	0.7	0.7
Amitriptyline / chlordiazepoxide-amitriptylline	Yes	2.0	2.0
Doxepin	Yes	0.1	0.1
Meprobamate	Yes	< 0.1	< 0.1
Long-acting benzodiazepines:	Yes		
flurazepam		0.5	0.5
chlordiazepoxide		0.2	0.2
diazepam		2.8	2.8
chlorazepate *			0.4
Disopyramide	Yes	0.1	0.1
Methyldopa / Methyldopa-hydrochlorothiazide	Yes	0.1	0.1
Belladonna alkaloids	Yes	0.3	0.3
Antihstamines and anticholinergics (hydroxyzine, cyproheptadine, promethazine, dexchlorpheniramine)	Yes	Hydro 0.3 Cypro < 0.1 Promethazine 0.9 Dexchlorphen. 0.1	Hydro 0.3 Cypro < 0.1 Promethazine 0.9 Dexchlorphen. 0.1
Barbiturates except phenobarbital	Yes	0.1	0.1
Ketorolac *	Yes		0.2
Daily fluoxetine *	Yes		0.4
Amiodarone *	Yes		0.7
Orphenadrine *	Yes		< 0.1
Nitrofurantoin *	Yes		4.5
Doxazosine *	Yes		0.5
Thioridazine *	Yes		< 0.1
Cyclandelate	No	< 0.1	< 0.1
Clonidine *	No		0.1
Cimetidine *	No		0.8
Isoxsuprine *	No		< 0.1
Propoxyphene and combination drugs	No	0.1	0.1
Phenylbutazone #	No	< 0.1	
Dipyridamole #	No	1.4	

* drugs added to list by 2002 criteria
# drugs removed from list by 2002 criteria

Table 3 Inappropriate drug prescribing considering maximum dose in year 2001, N=25,258

Type of medication	Maximum dose	Severe potential adverse effects	Patients prescribed drug, %	Overdosing in patients prescribed drug, %	Overdosing in study population, %
Lorazepam	3 mg	Yes	1.0	11.5	0.1
Oxazepam	60 mg	Yes	8.8	0.9	0.1
Alprazolam	2 mg	Yes	0.6	0	0
Temazepam	15 mg	Yes	6.7	29.6	2.0
Triazolam	0.25 mg	Yes	0	0	0
Zolpidem	5 mg	No	0.9	92.5	0.8
Iron #	325 mg	No	2.4	0	0
Ferrous sulfate *	325 mg	No	0.8	0	0
Reserpine *	0.25 mg	No	0	0	0
Digoxin	0.125 mg, except when treating atrial arrhythmias	No	4.3	12.2	0.5
Any of above			20.8	16.3	3.4

* drugs added to list by 2002 criteria
# drugs removed from list by 2002 criteria

Table 4 Inappropriate drug prescribing considering co-morbidity in year 2001, N=25,258

Disease and type of medication	Severe potential adverse effects	Patients prescribed drug, having the disease, %	
		Criteria 1997	**Criteria 2002**
Heart failure (n=1479)			
With disopyramide	Yes	0.1	0.1
With drugs with high sodium content	Yes	0.2	0.2
Diabetes receiving treatment (n=2777) #			
With beta-blockers		28.7	
Hypertension (n=5074)	Yes		
With amphetamines		0	0
With pseudoephedrine		0	0
With phenylpropanelamine		0	0
Chronic obstructive lung disease (n=1655)			
With propanolol	Yes		0
With long-acting benzodiazepines	Yes	3.9	3.9
With beta-blockers #		15.8	
Gastric/duodenal ulcers (n=1952)			
With NSAIDs	Yes	26.6	26.6
Epilepsy or seizures (n=139)			
With clozapine, chlorpromazine, thioridazine or chlorprothixene	Yes	0	0
With Bupropion *	Yes		0
Peripheral vascular disease (n=550) #			
With beta-blockers		24.4	
With metoclopramide		0.7	
Anticoagulant therapy (n=953)			
With aspirin	Yes	9.7	9.7
With NSAIDs	Yes	20.1	20.1
With dipyridamole, clopidrogel * or ticlopidine	Yes	3.8	3.8
Bladder outflow obstruction (n=1209)			
With anticholinergic antidepressants	Yes	4.3	4.3
With anticholinergic antihistamines	Yes	3.6	3.6
With gastrointestinal antispasmodics	Yes	0.1	0.1
With anticholinergics *	Yes		6.9
With decongestants *	Yes		2.4
With oxybutinin, flavoxate or tolterodine *	Yes		3.5

Table 4 (continued)

Disease and type of medication	Severe potential adverse effects	Patients prescribed drug, having the disease, %	
		Criteria 1997	**Criteria 2002**
Syncope or falls (n=560)			
With short-intermediate/long acting benzodiazepines	Yes	26.4	26.4
With tricyclic antidepressants	Yes	3.9	3.9
With beta-blockers #		20.9	
Arrhythmias (n=1198)			
With tricyclic antidepressants	Yes	2.3	2.3
Parkinson's disease (n=265) *	Yes		
With metoclopramide			1.5
With conventional antipsychotics			17.7
With tacrine			0
Cognitive impairment (n=196) *	Yes		
With barbiturates			0
With anticholinergics			3.5
With antispasmodics			0.5
With CNS stimulants			0

* co-morbidity/drugs added to list by 2002 criteria
# co-morbidity/drugs removed from list by 2002 criteria

Discussion

According to this population-based cohort study, one out of five ambulatory older adults receive at least one inappropriate drug prescription per year. This is the first study that applies all the categories of the Beers criteria and evaluates the impact of the updated criteria compared to the previously used 1997 criteria. Using the newest criteria, we observed that inappropriate drug prescribing remained rather stable over the years 1997-2001.

Compared to previous studies in the USA [1,5-7,13], the use of inappropriate drugs from the general 1997 list by older adults in the Netherlands is relatively low, but still substantial (9.3% in 2001, table 2). The use of inappropriate drugs from the general 1997 list was similar to what has been found in Finland [8]. However, when using the 1997 criteria including dose and co-morbidity, the risk of receiving inappropriate prescriptions almost doubles (18.5% in 2001, figure 1). This probably means that inappropriate drug use in the USA is significantly higher than around the estimated 20% [1,5-7], when dose and co-morbidity are included.

While considering dose, the drugs most frequently prescribed in a supratherapeutic dose in the Netherlands were zolpidem and temazepam (table 3). This finding was remarkable, because in our national drug information guides the recommended dose for temazepam in elderly is a maximum of 10 mg/day (normal dose 10-20 mg/day in adults) and for zolpidem 5 mg/day (normal dose 10 mg/day). Apparently, there is a huge gap between recommendations and clinical practice. We think that physicians should be made more conscious how to prescribe risky drugs in elderly. For example, a separate chapter in drug guides dealing with a list of risky drugs for the elderly and how (not) to prescribe these drugs, like the Beers criteria, could be an option to improve drug prescribing in this group.

While considering co-morbidity, we found relatively high risks for receiving inappropriate drugs: 26.6% of the elderly with (a history of) gastric/duodenal ulcer received conventional NSAIDs in 2001, most of them (> 80%) without concomitant gastro-protective drug [14]. This result is in line with an earlier finding by Visser et al. [15]. Furthermore, 26.4% of elderly with (previous) syncope or falls received benzodiazepines with a longer elimination half-life. As a result of updating the criteria, beta-blockers combined with asthma/COPD are no longer contra-indicated, except for propranolol. This is roughly in line with our national guidelines: only non-selective beta-blockers are contra-indicated in asthma/COPD patients. Indeed, we did not observe any asthma/COPD patients in our study population who were prescribed propranolol, while propranolol is a regularly prescribed drug in the Netherlands.

The Beers criteria have been criticized, since they do not identify all causes of potentially inappropriate prescribing (e.g. drug-drug interactions are not included)

and sometimes define appropriate prescribing as inappropriate [16]. Furthermore, the criteria only focus on prescribing inappropriate medications and not on potential underprescribing of indicated drugs and other drug management issues, such as medication monitoring and documentation [17]. This is a limitation of the Beers criteria. However, these criteria represent a widely used and standardized tool for pharmacological research, despite the fact that they can not be used as a substitute for careful clinical judgement [2].

Interestingly, the prevalences of inappropriate prescribing in the Netherlands and Finland seem to be remarkably lower than in the USA. However, 24 of the 78 drugs on the Beers list are not marketed in the Netherlands, some of which are commonly used in the USA. Hence, the differences in pharmaceutical marketing and drug policy among countries may have a great impact on the extent of inappropriate drug prescribing. On the other hand, the Beers list may not be complete enough to adequately assess inappropriate drug prescribing in Europe including the Netherlands. Drugs which could be inappropriate for older persons may be marketed in Europe and not included in the Beers list, because they are not marketed in the USA. Considering this, the extent of inappropriate drug prescribing observed in this study may be an underestimation of the real situation. We therefore propose to adjust the Beers criteria to European standards to be more useful in Europe. Still, we think the Beers criteria can give us a rough idea of inappropriate prescribing in medical practice.

Furthermore, it may be interesting to assess in future studies the consequences of inappropriate prescribing according to the Beers criteria, such as comparing the risk of falls and fractures in patient groups with and without inappropriate drug use. Comparing outcomes could give us an idea to what extent these criteria are relevant in clinical practice and influence the prognosis of older patients.

A limitation of this study is that the IPCI database may miss drug prescriptions that are directly written by medical specialists. However, in the Netherlands these prescriptions are commonly continued by the GP, especially if it concerns chronic medication use. Hence, prescription data include all GP prescriptions and prescriptions initiated by the specialists which are continued by the GP. Nevertheless, missing some of the specialist prescriptions could lead to an underestimation of the extent of inappropriate prescribing. Another limitation is that we may have overestimated inappropriate use, since we only have the prescription and not the dispensing data of the drugs. Pharmacists may have intercepted inappropriate prescribing with their medication surveillance system.

In conclusion, for this study we were able to use very comprehensive drug and diagnosis data to assess potentially inappropriate prescribing to older adults applying the most complete and recent Beers criteria. Despite a

restrictive medication policy and a growing attention for medication surveillance in Europe, inappropriate drug prescribing is still a substantial problem. Other aspects of medication care, such as underprescribing and drug monitoring and documentation, also deserve attention [17]. Therefore, for example, criteria that emphasize these aspects [18] and the Beers criteria should be applied in a complementary way, to improve drug prescribing in this vulnerable group.

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2.2

Inappropriate benzodiazepine use in older adults and the risk of fracture

Abstract

Background: The Beers criteria for inappropriate medication use in the elderly are well known and have been used for many drug utilization studies. However, the clinical value of these criteria has hardly been evaluated.
Objective: To investigate the clinical value of the Beers criteria for benzodiazepine use, by studying the association between inappropriate use and the risk of fracture.
Methods: We performed a nested case control study within the Rotterdam study, a population-based cohort study in 7983 older adults. The proportion of 'inappropriate' benzodiazepine use according to the Beers criteria was compared between fracture patients and controls. 'Inappropriate' use for elderly implies the use of some long-acting benzodiazepines and some intermediate/short-acting ones exceeding a suggested maximum daily dose. Also, alternative criteria were applied to compare the risk of fracture. Cases were defined as persons with incident fracture between 1991 and 2002 who were current benzodiazepine user on the fracture date. Controls were matched on fracture date and were also current benzodiazepine user.
Results: The risk of fracture in 'inappropriate' benzodiazepine users according to the Beers criteria compared to 'appropriate' users, was not significantly different (OR = 1.07 [95% CI: 0.72-1.60]). However, the risk of fracture in 'high dose' benzodiazepine users was significantly higher than the risk in 'low dose' users, regardless of the type of benzodiazepine (OR = 1.80 [95% CI: 1.16-2.78]). We found the highest risk of fracture in 'high dose' users and duration of use between 14 and 90 days (OR = 3.45 [95% CI: 1.38-8.59]).
Conclusions: These findings suggest that inappropriate benzodiazepine use according to the Beers criteria is not associated with an increased risk of fracture.

Introduction

Inappropriate medication use is a major concern, especially for the growing older population because it increases the risk of adverse drug reactions [1]. Inappropriate medication use for older adults is defined as medication use for which the potential harm outweighs the potential benefit and for which a good alternative is available [2].

In 1997, Beers and colleagues developed a comprehensive set of explicit criteria for potentially inappropriate drug use in ambulatory elderly, aged 65 years and over [2]. Drugs were classified as inappropriately prescribed, when they fulfilled one of the following criteria: 1) drugs that generally should be avoided in older adults, 2) drugs that exceed a maximum recommended daily dose and 3) drugs to be avoided in combination with specific co-morbidity. These criteria were developed with the intent to be applicable to any population of persons older than 65 years, regardless of their level of frailty or their place of residence. Recently, Beers et al. presented the results of the updated 1997 criteria by a US consensus panel of experts, based on scientific literature and new insights [3].

The Beers criteria have been criticized, since they do not identify all causes of potentially inappropriate prescribing and sometimes define appropriate prescribing as inappropriate [4]. Moreover, the relevance of using these criteria in clinical practice is unproven because they still have not been properly validated in patient outcome studies.

The Beers criteria contain statements about use of benzodiazepines. In short, some long-acting benzodiazepines should not be prescribed to older adults and some intermediate/short-acting benzodiazepines should preferably not exceed a proposed maximum daily dose. The potential adverse effects of this inappropriate prescribing are prolonged sedation and increased incidence of falls and fractures [3].

A recent review of observational studies assessing the association between use of benzodiazepines and risk of hip fracture, concluded that use of benzodiazepines by older people increases their risk of hip fracture by at least 50%. However, it is controversial whether the risk of hip fracture differs between short- and long-acting benzodiazepine users and the authors concluded that there is more evidence that people using higher doses of benzodiazepines and those having recently started are at highest risk, regardless of the type of benzodiazepine [5].

Therefore, we performed a nested case control study in a cohort of benzodiazepine users of 65 years and older, to compare the risk of fracture by applying the Beers criteria and by applying alternative criteria based on daily dose, elimination half-life and duration of use, respectively.

Methods

Setting

This study was conducted as part of the Rotterdam Study, a prospective population-based cohort study on the occurrence and determinants of disease and disability in elderly persons [6]. In 1990, all inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, who were 55 years of age or older and had lived in the district for at least 1 year were invited to participate in the study. Of the 10275 eligible persons, 7983 (78%) participated. Participants gave informed consent and permission to retrieve information from medical records. At baseline, between 1990 and 1993, trained interviewers administered an extensive questionnaire covering socio-economic background and medical history, among other topics, during a home interview. During subsequent visits to the study center, additional interviewing, laboratory assessments, and clinical examinations were performed. Information on vital status is obtained at regular time intervals from the municipal authorities in Rotterdam. The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study.

Case and control definition

The study participants' general practitioners report all fatal and nonfatal events, such as fractures, through a computerized system. These data cover approximately 80% of the study sample. For participants who were not covered in this system, research physicians performed annual checks on the complete medical records of all general practitioners in the Rotterdam Study.

Two research physicians independently coded all fractures that occurred during the study period using the International Classification of Diseases, 10th revision (ICD-10) [7]. A medical expert in the field who was unaware of the patients' history and medication use reviewed all coded events for a final classification. For the present study, all participants were followed from 1 January 1991 until they had an incident fracture, died, or reached the end of the study at 31 December 2001, whichever came first. Pathologic fractures (M84.4), vertebral fractures (S22.0, S22.1 and S32.0) and fractures in prosthetic hips (M96.6) were excluded. Accordingly, 1224 incident fractures were detected.

The date of fracture occurrence was defined as the index date. Cases were defined as persons with an incident fracture between 1 January 1991 and 31 December 2001 who were current benzodiazepine user and aged 65 years or older on the index date. From the 1224 incident fracture patients, 200 cases were identified. To each case, we matched all persons aged 65 years or older who were current benzodiazepine users on the index date of the corresponding case and

who were at risk for fracture. Consequently, cases and controls had to be current benzodiazepine users for at least one day before the index date.

Exposure definition

In the research area, there are 7 fully computerized pharmacies that are linked to 1 network. During the study, all participants filled their prescriptions in 1 of these 7 pharmacies. Data on all dispensed drugs since 1 January 1991 are available in computerized format on a day-to-day basis. The data include the date of prescribing, the total amount of drug units per prescription, the prescribed daily number of units, product name, and the Anatomical Therapeutic Chemical (ATC) code [8].

Current use of benzodiazepines at the index date was retrieved from these prescription records. The exposure of interest included current use of the following benzodiazepines: lorazepam, oxazepam, alprazolam, temazepam, triazolam, diazepam, flurazepam, clorazepate, chlordiazepoxide, medazepam, quazepam, bromazepam, clobazam, ketazolam, prazepam, nitrazepam, flunitrazepam, lormetazepam, midazolam, brotizolam, and loprazolam. These benzodiazepines were at least once prescribed to any of the study participants during the study period.

To compare the proportion of 'inappropriate' benzodiazepine use according to the Beers criteria between cases of fracture and controls, we defined all current benzodiazepine users at the index date as 'inappropriate' or 'appropriate' users. 'Inappropriate' users fulfilled the 2002 Beers criteria for inappropriate benzodiazepine use [3] (**table 1**). Users who did not fulfil the Beers criteria for inappropriate benzodiazepine use, were defined as 'appropriate'.

In a second analysis, we studied the effect of dosage (high versus low) on the risk of fracture, regardless of what type of benzodiazepine was prescribed. We defined the benzodiazepine users with a daily dose higher than 10 mg of diazepam dose equivalents as 'high dose' and equal or less than 10 mg of diazepam dose equivalents as 'low dose' users.

Subsequently, we studied the effect of elimination half-life (long versus short) on the risk of fracture. For this analysis we defined users of benzodiazepines with an elimination half life >24 hours as 'long-acting' and ≤ 24 hours as 'short-acting' benzodiazepine users [9,10]. Consequently, we judged diazepam, flurazepam, clorazepate, chlordiazepoxide, quazepam, clobazam, ketazolam and prazepam as long-acting benzodiazepines. The other benzodiazepines prescribed to the study participants were judged as 'short-acting'.

The effect of duration of use on the risk of fracture was assessed by dividing current use in 3 mutually exclusive groups: 14 days or less (short-term use), use between 14 and 90 days (intermediate-term use) and use longer than 90 days (long-term or chronic use).

Cofactors

The following baseline patient characteristics, all determined by interview or during the visit to the examination center, were individually assessed as potential confounders: age, sex, use of a walking aid, any fracture in the 5 years before baseline, rheumatoid arthritis, frequency of falling (≥ once per month), current smoking, intake of alcohol (g/day), dizziness, visual impairment, Parkinson disease, hypertension, diabetes mellitus, presence of peripheral arterial disease, and body mass index. For assessment of prevalent dementia at baseline, participants were cognitively screened. Screen-positives underwent further cognitive testing, which has been described in detail elsewhere [11]. Lower-limb disability was assessed by using a modified version of the Stanford Health Assessment Questionnaire [12] and by calculating the mean score of answers to questions about rising, walking, bending, and getting in and out of a car [13]. The score ranges from 0 (no disability) to 3 (severe disability). Bone mineral density of the femoral neck was measured by using dual-energy X-ray absorptiometry (DPX-L densitometer, Lunar Corp., Madison, Wisconsin), as described elsewhere [14].

Use of other medications on the index date, such as antidepressants, anticonvulsants, antihistamines, antipsychotics, opioids, barbiturates, antacids, diuretics, beta-blockers, corticosteroids, statins and the amount of prescribed medications, was obtained from pharmacy records and analyzed as a potential confounder. While applying the alternative criteria to investigate the association between benzodiazepine use and fractures, daily dose, elimination half-life and duration of use of the benzodiazepines were also analyzed as potential confounder in the different exposure models.

Statistical analysis

The incidence rate of fracture in benzodiazepine users was calculated using the number of cases as the numerator and the total number of person-years of benzodiazepine use during the study period as denominator.

Conditional logistic regression analyses were performed to estimate the crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). To adjust for potential confounders, cofactors associated with the occurrence of fracture were included one-by-one in the age- and sex-adjusted model. Cofactors that changed the OR for fracture during use of benzodiazepines by more than 5% or that were biologically plausible were maintained in the final model. In an extra analysis, we used missing value indicators for missing values of cofactors to prevent exclusion of cases with incomplete data and to evaluate potential confounding by missing values. Cofactors with missing values were therefore categorized, with a separate category for missing values. Accordingly, missing values were incorporated in

the statistical model to investigate whether the missing status confounded the association of interest.

To test for effect modification by cofactors such as age, sex, alcohol use, body mass index, elimination half-life, daily dose and duration of use, interaction terms were introduced in the statistical model and separate analyses were performed in the different categories. All statistical analyses were performed using SPSS-PC version 11.0 (SPSS Inc., 1989 – 2001).

Results

The incidence rate of fracture in benzodiazepine users during the study period was 2.9 per 100 person-years. Baseline characteristics of cases and controls are shown in **table 2**. There were 200 cases and 2678 controls. Of the cases, 70 patients had a hip fracture, 43 patients a wrist fracture and 87 patients 'other' fractures, such as tibia, hand, foot and skull. At baseline, the proportion of females, and mean age were higher in cases than in controls. Cases were more likely to have dementia at baseline, and had a relatively lower BMD, adjusted for age and sex.

'Inappropriate' benzodiazepine use according to the Beers criteria was similar in cases and controls (OR = 1.02 [95% CI: 0.75-1.38]) **table 3**). In subsequent analyses, we used alternative criteria for 'inappropriate' use based on the existing literature. The risk of fracture in 'high dose' users was significantly higher than the risk in 'low dose' users (OR = 1.57 [95% CI: 1.11-2.18]) **table 3**). After additional adjustments for age, sex, dementia, alcohol intake, BMI and BMD (the final model), the risk of fracture was still statistically significantly different (OR = 1.80 [95% CI: 1.16-2.78]). Studying the effect of use of long- versus short-acting benzodiazepines, we did not find a statistically significant difference on the risk of fracture (OR = 1.23 [95% CI: 0.73-2.08]). However, when assessing the duration of use, people using between 14 and 90 days had a significantly higher risk of fracture than people using ≤ 14 days (OR = 2.15 [95% CI: 1.14-4.08], table 3).

In additional analyses in different categories, we found the highest odds ratio for the risk of fracture in the group of persons with a high daily dose and a duration of use between 14 and 90 days compared to persons with a low daily dose and duration of use of 14 days or less (OR = 3.45 [95% CI: 1.38-8.59], **table 4**).

Body mass index appeared to be an effect modifier by dividing the study sample at the median observation (26 kg/m2). When assessing the risk of fracture in high versus low dose benzodiazepine users, we found only a statistically significant effect in people with relatively low BMI (< 26 kg/m2), adjusted for age, sex, dementia, alcohol intake and bone mineral density (OR = 2.44 [95% CI: 1.40-4.24]).

After adjustment for missing values, the risk of fracture in 'high dose' users was somewhat lower but still significant with an OR of 1.69 (95% CI: 1.20-2.38). Similarly, for duration of use between 14 and 90 days the OR was 1.67 (95% CI: 1.07-2.62). The OR in persons with a high daily dose and duration of use between 14 and 90 days was 2.33 (95% CI: 1.16-4.67).

Table 1 Beers criteria for inappropriate benzodiazepine use in older adults *

Type of benzodiazepine #	Daily dose
Short-acting	
lorazepam	> 3 mg
oxazepam	> 60 mg
alprazolam	> 2 mg
temazepam	> 15 mg
triazolam	> 0.25 mg
Long-acting	
diazepam	do not prescribe
flurazepam	do not prescribe
clorazepate	do not prescribe
chlordiazepoxide	do not prescribe
Quazepam	do not prescribe
halazepam ^	do not prescribe
chlordiazepoxide-amitriptyline ^	do not prescribe
clidinium-chlordiazepoxide ^	do not prescribe

* according to the 2002 Beers criteria [3]
# severity of inappropriate use for each of the medications is rated as 'high' [3]
^ not prescribed in this study population

Table 2 Baseline characteristics of the study population

Characteristic	Cases (n = 200)	Controls (n = 2678)	OR* (95% CI)	Subjects with missing values (%)
Sex				
women	174 (87%)	1884 (70%)	1.68 (1.11–2.54)	0
Age, year #	76.6 ± 8.51	74.9 ± 8.04	1.04 (1.02–1.06)	0
BMI, kg/m2 #	26.3 ± 3.90	26.5 ± 3.89	0.97 (0.94–1.01)	14
Femoral neck BMD #	0.74 ± 0.14	0.81 ± 0.14	0.04 (0.01–0.15)	29
History of fracture (in 5 years before baseline)	37 (19%)	374 (14%)	1.14 (0.79–1.63)	8
Falling ≥ 1x/month	8 (4%)	76 (3%)	1.68 (0.83–3.43)	4
Current smoking	41 (21%)	509 (19%)	1.26 (0.87 – 1.83)	5
Alcohol intake > 2 g/day	57 (29%)	830 (31%)	1.16 (0.81 - 1.67)	35
Dementia	18 (14%)	186 (7%)	1.77 (1.05 - 2.00)	6
Parkinsonism **	9 (5%)	68 (3%)	1.76 (0.90 - 3.44)	< 1
Lower-limb disability score #	0.83 ± 0.79	0.63 ± 0.74	1.12 (0.91–2.55)	3
Use of walking aid	42 (21%)	430 (16%)	0.92 (0.80 - 1.07)	9

* OR for fracture, age- and sex adjusted; # mean ± SD; ** includes Parkinson disease
BMD = bone mineral density; BMI = body mass index

Table 3 Odds Ratio (OR) for fracture based on different criteria for benzodiazepine use

Exposure on index date	Cases (n = 200)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Beers criteria			
Appropriate, n (%)	140 (70%)	1.00 (reference)	1.00 (reference)
Inappropriate, n (%)	60 (30%)	1.02 (0.75–1.38)	1.07 (0.72–1.60)
Daily dose**			
Low, n (%)	157 (78%)	1.00 (reference)	1.00 (reference)
High, n (%)	43 (22%)	1.57 (1.11–2.18)	**1.80 (1.16–2.78)**
Type (half-life)			
Short-acting (≤ 24 h)	176 (88%)	1.00 (reference)	1.00 (reference)
Long-acting (> 24 h) #	24 (12%)	0.90 (0.59–1.38)	1.23 (0.73–2.08)
Duration of use			
≤ 14 days	25 (13%)	1.00 (reference)	1.00 (reference)
14 - 90 days	82 (41%)	1.72 (1.10–2.69)	**2.15 (1.14–4.08)**
> 90 days	93 (46%)	1.19 (0.77–1.85)	1.70 (0.91–3.20)

* adjusted for age, sex, dementia, alcohol intake, body mass index and bone mineral density
** high: > 10 mg of diazepam equivalents
# diazepam, flurazepam, clorazepate, chlordiazepoxide, quazepam, clobazam, ketazolam and prazepam

Table 4 Odds Ratio* (95% CI) for fracture in different categories of benzodiazepine users: Interaction of daily dose and duration of use

	Daily dose Low	High**
Duration of use		
≤ 14 days	1.00 (reference) (24)#	0.96 (0.12–7.42) (1)#
14 - 90 days	**1.98 (1.01–3.89)** (70)#	**3.45 (1.38–8.59)** (12)#
> 90 days	1.42 (0.72–2.80) (63)#	**2.79 (1.31–5.93)** (30)#

* adjusted for age, sex, dementia, alcohol intake, body mass index and bone mineral density
** high: > 10 mg of diazepam equivalents
# number of cases

Discussion

In this population-based study of community-dwelling elderly, the risk of fracture was not different between persons with 'inappropriate' benzodiazepine use, according to the Beers criteria, and persons with 'appropriate' benzodiazepine use. This finding suggests that the Beers criteria for benzodiazepine use are not clinically relevant regarding the risk of fracture. However, using other criteria based on the more recent insights in the literature, i.e. dose and duration of use being more important than type of benzodiazepine [5,10,15,16], we found that the risk of fracture significantly increases in persons with a high daily dose and longer duration of use compared to those on a low daily dose and a short duration of use (14 days or less), regardless of the type of benzodiazepine prescribed (OR = 3.45 (95% CI: 1.38-8.59)). These results seem to indicate that dosage and duration of use are more important criteria for appropriate benzodiazepine use in clinical practice than the Beers criteria, which are only focussing on elimination half-life and dosage of specific benzodiazepines.

We were not able to confirm the findings from earlier studies [10,15,16] and published clinical information that adverse effects usually occur during the first few days of benzodiazepine use. Possibly, users of benzodiazepines have to accumulate the drug or active metabolites up to a certain level at receptor sites before adverse effects such as prolonged sedation occur. Alternatively, patients may be still alert during the first two weeks of use because they have been warned against central nervous system effects by their doctor or pharmacist. After a couple of weeks, they might become less attentive and develop an increased risk of falling. However, we found a trend of decreasing risk again in chronic users (>90 days of use, table 3), possibly because these people get less sensitive to the sedation effects (receptor down-regulation) or it may be the consequence of 'depletion of susceptibles' ('healthy user effect').

Regarding effect modification, we found that especially in elderly with a lower BMI (< 26 kg/m2) the effect of daily dose on the risk of fracture is high. This is not surprising, because these persons have a higher risk of fracture when falling (greater impact of force on bone) compared to persons with a higher BMI and this group is more sensitive to higher doses of drugs.

Several aspects of validity need to be discussed. Selection bias is unlikely because cases and controls were derived from a prospective population-based cohort study, and controls came from the same study base as cases. Information bias is unlikely as data on drug use were prospectively gathered. As benzodiazepines are only available on prescription, pharmacy records provide complete coverage. Although we do not know if the patients really took the benzodiazepines as

prescribed and dispensed, compliance to benzodiazepines is usually high. Misclassification of fractures is unlikely and would be non-differential, because the outcome was assessed independently of the exposure. Hence, this could not lead to an overestimation of the risk.

As far as we know, this is the first study that investigated the effects of dose and duration within benzodiazepine users, which means that confounding (by indication) is less likely. Other observational studies that also investigated dose and duration effects of benzodiazepine use on the risk of fracture, almost always used non-users as the reference group. In these studies, confounding (by indication) is a potential problem: the amount and differences in patient characteristics related to exposure and outcome are probably greater between users versus non-users, and thus more difficult to adjust for. In our study, it is unlikely that confounding explains our results, because we were able to adjust for many potential confounders. To take into account potential confounding by missing value status of cofactors, we performed an extra analysis using missing value indicators in the adjusted model. In this analysis, the associations were less strong but still statistically significant. As we suspect that missing value status is non-random in this population, we did not perform (multiple) imputation of missing values. People who are more ill and less mobile tended to have more missing values, for instance because they were not able to come to the research center where several measurements had to be performed. This might be a reason that taking into account missing status slightly affected the results.

Almost 80% of the invited persons participated in the Rotterdam Study. The remaining non-participants were slightly older. Although we had no information about the morbidity in non-participants, it is possible that they were sicker. There is no reason to believe that this affected our internal validity, but it might have affected the generalizability of our results.

In conclusion, we were unable to demonstrate that the Beers criteria for benzodiazepine use are clinically relevant regarding the risk of fracture. However, based on the findings in this study, we may conclude that, when prescribing benzodiazepines to elderly, a high daily dose and a longer duration of use (>14 days), is 'inappropriate' regarding the risk of fracture, irrespective of the type of benzodiazepine prescribed. Consequently, if a benzodiazepine is indicated for an older person, physicians should prescribe a lower (geriatric) dose and for a time period as short as possible to reduce the risk of fracture.

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3

Hospitalisations related to adverse drug reactions (ADRs)

3.1

ADR-related hospitalisations: a nationwide study in the Netherlands

Abstract

Background: The incidence of Adverse Drug Reaction (ADR)-related hospitalisations has usually been assessed within hospitals. Because of the variability in results and methodology, it is difficult to extrapolate these results to a national level.
Objective: To evaluate the incidence and characteristics of ADR-related hospitalisations in the Netherlands in 2001.
Methods: We conducted a nationwide study of all hospital admissions in 2001. Data were retrieved from a nationwide computer database for hospital discharge records. All acute, non-planned admissions to all Dutch academic and general hospitals in 2001 were included in the study (n=668,714). From these admissions we selected all hospitalisations that were coded as drug-related but intended forms of overdose, errors in administration and therapeutic failures were excluded. Hence, we extracted all ADR-related hospitalisations. We compared age, sex and the risk of a fatal outcome between patients admitted with ADRs and patients admitted for other reasons. Furthermore, we evaluated to what extent these ADRs were reported to the Netherlands Pharmacovigilance Centre for spontaneous ADR reporting.
Results: In 2001, 12,249 hospitalisations were coded as ADR-related. This was 1.83% of all acute hospital admissions in the Netherlands (95% CI: 1.80-1.86%). The proportion increased with age from 0.8% (0.75- 0.85%) in the age group below 18 years to 3.2% in the age group of 80 years and older (3.08-3.32%). The most frequent ADR-related diagnoses of hospitalisations were bleeding (n=1048), non-specified 'unintended effect of drug' (n=438), hypoglycemia (n=375) and fever (n=347). Drugs most commonly associated with ADR-related hospitalisations were anticoagulants (n=2185), 'cytostatics and immunosuppressives' (n=1809) and diuretics (n=979). Six percent of the ADR-related hospitalisations had a fatal outcome (n=734). Older age and female gender were associated with ADR-related hospitalisations. Only about 1% of the coded ADRs causing hospitalisation was reported to our national centre for spontaneous ADR reporting.
Conclusions: The proportion of ADR-related hospitalisations is substantial, especially considering the fact that not all ADRs may be recognized or mentioned in discharge letters. Underreporting of ADRs causing hospital admission to our national centre for spontaneous ADR reporting was considerable.

Introduction

Studies have estimated a wide variation in frequencies of ADR-related hospitalisations. Meta-analyses have estimated that hospitalisations attributed to adverse drug reactions (ADRs) account for between 2.4 % and 6.4 % of all hospital admissions in Western countries [1-5]. For the elderly this percentage has been estimated between 3.4 % and 16.6 % [4,6]. Approximately 80% of ADRs causing admission or occurring in hospital are type A (dose-related) reactions, and thus predictable from the known pharmacology of the drug and therefore potentially avoidable [2,7]. Most epidemiological studies evaluating the extent of ADR-related hospitalisations were conducted within (single) units, departments or hospitals, hence different settings and methods were used. Because of the variability of the results and methodology and a lack of representativeness, it is difficult to confidently extrapolate these results to a national level. In 1998, a national prospective cross-sectional study was performed in France [8]. However, only a nationwide sample of medical wards in public hospitals was taken and studied for 14 days to estimate their national incidence of ADR-related hospitalisations. To estimate our national incidence of ADR-related hospitalisations, we conducted a study of all hospital admissions in the Netherlands in 2001. To our knowledge, this is the first nationwide study performed to evaluate ADR-related hospitalisations

Methods

Data were retrieved from a nationwide computer database for hospital discharge records, containing among others basic patient characteristics, date of admission and discharge, discharge / main diagnosis (coded), secondary diagnoses (coded), medical specialism (coded) and special codes indicating drug-related hospitalisations (E-codes), based on the ICD-9-CM coding system [9]. Characteristics of all hospitalisations are registered by medical doctors on the basis of hospital discharge letters and coded by professional code clerks. For every admission, one discharge / main diagnosis (mandatory), and up to 9 secondary diagnoses (optional) are registered. The coding is independent of reimbursement of hospital or specialist. All diagnoses are submitted in the same format, mostly electronically.

All patients with an acute, non-planned admission to a Dutch hospital in 2001 were included in the study (n =668,714). An ADR-related hospitalisation was defined as a hospitalisation with an E-code, indicating an ADR as the reason for hospitalisation (E-code referring to main diagnosis) or an ADR occurring during a hospitalisation (E-code referring to secondary diagnosis). The E-code does indicate

the drug group involved. Intended forms of overdose, errors in administration and therapeutic failures were not included.

We assessed the proportion of ADR-related hospitalisations of all acute admissions in all Dutch academic (n=8) and general (n=100) hospitals, in a subset of acute admissions to the departments internal medicine, pediatrics, cardiology, lung diseases, gastro-enterology and clinical geriatrics and in different age groups. We also assessed what were the most frequent main diagnoses in ADR-related hospitalisations and which drugs most frequently caused the ADRs. We compared age, sex, duration of hospital stay and the risk of a fatal outcome between patients with ADR-related hospitalisations and patients with other acute admissions.

Furthermore, we evaluated in the ADR-related hospitalisations with the E-code directly referring to the main diagnosis (n=6209), to what extent these ADRs were reported to the Netherlands Pharmacovigilance Centre Lareb for spontaneous ADR reporting. All Dutch health care providers are recommended to report serious ADRs to Lareb, such as ADRs leading to hospitalisation, permanent disability or death [10]. It is known that underreporting of ADRs exists in a spontaneous reporting system and that signal detecting of new and serious ADRs is mainly the aim of such a system [11]. However, little is known about the extent of underreporting of serious ADRs in the Netherlands [12]. Therefore the national hospital discharge records of 2001 were linked by sex and birth date to the Lareb database of spontaneous ADR reports in 2001. If the reported ADR, discharge diagnosis and the corresponding drug matched well and the date of ADR reporting was within one month after or two weeks before the date of admission, we assumed this to be the same case and classified this ADR-related admission to be reported to Lareb.

The ethical review board of the institution which holds the database gave consent for performing this study.

Descriptive analyses were conducted in SPSS 11.0. Statistical comparison consisted of standard t-tests (unpaired) and Chi square-tests. A Mann-Whitney test was used for non-normally distributed data. Ninety five percent confidence intervals around estimates were calculated based on a binomial distribution.

Results

The baseline characteristics of the study population are shown in **table 1**. The mean age of people with acute, non-planned admissions was 48 years and 53.4% were female. The most frequent main diagnoses of acute admissions were 'chest pain' (5.3 %), ' abdominal pain' (2.8%), and pneumonia (1.8%). A number of 12,249 hospitalisations were coded as ADR-related; of those, 6209 admissions were coded

as an ADR-related main diagnosis. Based on this number (12,249), the incidence of ADR-related hospitalisations in the Netherlands was 76,3 /100,000 inhabitants in 2001. The proportion of ADR-related hospitalisations was 1.83% of all acute, non-planned hospital admissions in the Netherlands (95% CI: 1.80% to 1.86%). A number of 734 patients (6%) died during an ADR-related hospitalisation.

In the age group of persons younger than 18 years the proportion of ADR-related hospitalisations was 0.8% (0.75% to 0.85%), 1.32% (1.28% to 1.36%) in the age group 18 - 64 years, 2.81% (2.73% to 2.89%) in the age group 65 – 79, and 3.2% (3.08% to 3.32%) in the age group of 80 years and older (**table 2**). In a subselection of all acute admissions to departments of internal medicine, pediatrics, cardiology, lung diseases, gastro-enterology and clinical geriatrics (n=353,688), the proportion was 2.84% (95% CI: 2.79% to 2.89%). In people aged 65 years and older it increased to 3.75% (3.66% to 3.84%) and it was 4.29% (4.12% to 4.46%) in persons aged 80 years and older (table 2). We also assessed the proportion in this subselection because most patients with ADR-related problems are admitted to these departments and many other studies in this field were performed within one or more of these departments.

The proportion of ADR-related hospitalisations was 1.2% in academic hospitals as against 1.9% in general hospitals. The difference increased with advancing age: 1.9% versus 3.3% in people of 80 years and older (for these comparisons, $p<0.001$).

The most frequent main diagnoses of ADR-related hospitalisations are shown in **table 3**: bleeding diagnoses (gastrointestinal bleeding, n=436; non-specified bleeding, n=264; intracerebral bleeding, n=178; chronic ulcus ventriculi with bleeding, n=170), non-specified 'unintended effect of drug' (n=438), hypoglycemia (n=375), fever (n=347), agranulocytosis (n=271) and dehydration (n=255) . The drugs most commonly associated with ADR-related hospitalisations were anticoagulants (n=2185), 'cytostatics and immunosuppressives' (n=1809), diuretics (n=979), 'insuline and antidiabetics' (n=541), salicylates (n=509) and antirheumatics (n=496).

The mean age of patients with ADR-related hospitalisations was 62 years as against 48 years in other admissions, 55.2% were female versus 53.4% in other admissions ($p<0.001$), and 6.0% died during hospitalisation as against 5.6% during non-ADR-related hospitalisations ($p<0.05$) (**table 4**). This gender associated risk increased with increasing age but the fatality rate diminished. In the age group 65 - 79 years, 50.5% of the patients with ADR-related hospitalisations were female as against 46.1% in other admissions. Approximately 8% died during ADR-related hospitalisations as against 9.8% during other acute admissions. In the highest age group (80 years and older), 66.6% was female versus 62.9% in other admissions and 9.7% died during hospitalisation versus 16.5% during acute hospitalisations for other reasons (for these comparisons, $p<0.001$).

The mean duration of ADR-related hospitalisations was 12.5 days as against 10 days in other acute admissions (p<0.001). In the age group 65 years and older, no significant difference was found anymore in mean duration of hospital stay (data not shown).

Only 59 of the 6209 admissions with a coded ADR-related main diagnosis in 2001 were reported to our national Pharmacovigilance Centre for spontaneous ADR reporting. This is about 1% (95% CI: 0.71% to 1.19%) of all hospitalisations that were caused by an ADR (59/6209). The most reported ADRs were angio-oedema (7/59), anaphylaxis (5/59) and hepatitis (5/59). The drug most reported to cause an ADR was nitrofurantoin (5/59).

Table 1 Baseline characteristics of study population (n = 668,714)

Characteristic	
Mean age (years)	48.4
Female sex, %	53.4
Most frequent main diagnoses (% of hospitalisations)	Chest pain (5.3) Abdominal pain (2.8) Pneumonia (1.8) Atrial fibrillation (1.6) Chronic obstructive lung disease (1.5)
Median duration of admission in days (interquartile range)	5.0 (2.0–11.0)
Died during admission, %	5.6
ADR-related diagnoses, %	1.8

Table 2 Percentage of ADR-related hospitalisations in 2001 in different age groups

ADR-related hospitalisations (all)		
Age	**Percentage, % (n)**	**95% CI**
< 18 years (n = 109,047)	0.80 (871)	0.75 - 0.85
18 – 64 years (n = 314,208)	1.32 (4145)	1.28 - 1.36
65 – 79 years (n = 159,117)	2.81 (4467)	2.73 - 2.89
ffl 80 years (n = 86,342)	3.20 (2766)	3.08 - 3.32
Total (n = 668,714)	1.83 (12,249)	1.80 - 1.86
ADR-related hospitalisations*		
Age	**Percentage, % (n)**	**95% CI**
< 18 years (n = 74,824)	1.12 (838)	1.04 - 1.20
18 – 64 years (n = 120,885)	2.71 (3276)	2.62 - 2.80
65 – 79 years (n = 105,163)	3.48 (3660)	3.37 - 3.59
ffl 80 years (n = 52,816)	4.29 (2266)	4.12 - 4.46
Total (n = 353,688)	2.84 (10,040)	2.79 - 2.89

* departments of internal medicine, pediatrics, cardiology, lung diseases, gastro-enterology and clinical geriatrics

Table 3 Most frequent main diagnoses and drug groups most commonly associated with the ADR in ADR-related hospitalisations (n=12,249)

Characteristic	ICD-9-CM code	Frequency	Percentage, %
Main diagnosis			
Gastrointestinal bleeding	578	436	
Non-specified bleeding	459.0	264	
Intracerebral bleeding	431	178	
Chronic ulcus ventriculi with bleeding	531.4	170	
Sum		1048	8.6
'Unintended effect of drug'	995.2	438	3.6
Hypoglycemia	251.2	375	3.1
Fever	780.6	347	2.8
Agranulocytosis	288.0	271	2.2
Dehydration	276.5	255	2.1
Drug group			
Anticoagulants	E934.2	2185	17.8
Cytostatics and immunosuppressives	E933 1	1809	14.8
Diuretics	E944.4	979	8.0
Insuline and antidiabetics	E932.3	541	4.4
Salicylates	E935.3	509	4.2
Antirheumatics	E935.6	496	4.1

Table 4 ADR-related hospitalisations compared to other acute admissions in different age groups

Characteristic	ADR-related hospitalisations	Other admissions	p-value *
< 18 years (n = 109,047)			
Mean age (years)	4.5	3.8	< 0.001
Female sex, %	46.4	44.2	NS
Mean duration of hospital stay (days)	3.6	5.8	< 0.001
Died during hospitalisation, %	0.4	0.5	NS
18 – 64 years (n = 314,208)			
Mean age (years)	47.5	41.7	< 0.001
Female sex, %	54.5	57.6	< 0.001
Mean duration of hospital stay (days)	9.7	7.6	< 0.001
Died during hospitalisation, %	2.7	2.3	NS
65 – 79 years (n = 159,117)			
Mean age (years)	72.8	72.4	< 0.001
Female sex, %	50.5	46.1	< 0.001
Mean duration of hospital stay (days)	14.3	13.5	< 0.01
Died during hospitalisation, %	7.9	9.8	< 0.001
80 years and over (n = 86,342)			
Mean age (years)	84.7	84.9	< 0.05
Female sex, %	66.6	62.9	< 0.001
Mean duration of hospital stay (days)	16.5	16.7	NS
Died during hospitalisation, %	9.7	16.5	< 0.001
Total (n = 668,714)			
Mean age (years)	62.1	48.2	< 0.001
Female sex, %	55.2	53.4	< 0.001
Mean duration of hospital stay (days)	12.5	9.9	< 0.001
Died during hospitalisation, %	6.0	5.6	< 0.05

* NS = not significant, cut off p-value: 0.05

Discussion

In this nationwide study, we found that 12,249 hospital admissions were ADR-related (almost 2% of all acute admissions in 2001). As suggested in other studies, this could mean that about 80% or even more of the ADRs that caused or complicated these 12,249 hospitalisations were potentially avoidable because they were type A (dose-related) reactions, and thus predictable from the known pharmacology of the drug [2,7]. Although the suggested preventability is disputable, this study can help us to identify the most frequent ADRs related to hospitalisations, study their nature and target on these ADRs to take preventive actions.

Six percent of the ADR-related hospitalisations had a fatal outcome (n=734) although it is unknown what the definite cause of death was. We found that the proportion of ADR-related hospitalisations increased with age from 0.8% in the age group below 18 years to 3.2% in the age group of 80 years and older, confirming that older persons have more ADR-related problems. In the subselection of all acute admissions to departments of internal medicine, pediatrics, cardiology, lung diseases, gastro-enterology and clinical geriatrics, the proportion increased from 1.1% in youngest age group to 4.3% in the eldest one.

The strength of the database that we used is that it includes all admissions in all Dutch general and university hospitals and that the admission codes are independent of reimbursement. The latter may be a problem in similar databases in some countries (e.g. the USA) where some diagnoses pay better than others. Our estimates are in general lower than in previous studies. Some (smaller) studies come to higher estimations but most of these studies investigate admissions in specific departments (such as internal medicine and cardiology) and assess all admissions with the prior hypothesis that drugs may have played a role [13-16]. Such studies might tend to overestimate the proportion of ADR-related hospitalisations. Indeed, it was found that smaller studies show higher proportions of ADR-related hospitalisations while larger studies display lower proportions [4].

As in other studies, we found that older age and female sex are associated with more ADR-related hospitalisations. This does not necessarily indicate that increasing age per se is a risk factor for the occurrence of ADRs. Several studies have clearly shown that the risk of ADRs (including interactions) is related to the number of drugs taken [17-19] and that the elderly receive more drugs, sometimes inappropriately [20,21].

In the total group, it seemed that slightly more people died during an ADR-related hospitalisation than during non-ADR-related hospitalisations (6.0% versus 5.6%, $p < 0.05$). However, we found that in the elderly (ffl 65 years) fewer people died during an ADR-related hospitalisation than during other acute ionshospitalisations (8.6% versus 12.2%, $p < 0.001$), indicating that the other

hospitalisations were probably for more serious conditions and/or ADRs were better to treat. It seems that ADR-related hospitalisations in the elderly are in general less life-threatening than other acute admissions of diseased elderly.

The mean duration of hospital stay in patients with ADR-related admissions was longer than in other acute admissions in the total group (12.5 days versus 9.9 days, $p < 0.001$). This difference disappeared in patients aged 65 and older (data not shown). The difference is mainly due to the ADR-related hospitalisations in younger persons (aged 18-64 y) who probably need a relatively longer hospital stay in these than in other hospitalisations which are usually short and non-complex in this age group (f.e. appendix surgery).

Only 1% of all ADR-related hospitalisations (with an ADR as main diagnosis) were reported to our national Pharmacovigilance Centre for spontaneous ADR reporting. All Dutch health care providers are recommended to report serious ADRs, such as ADRs leading to hospitalisation, permanent disability or death [10]. However, according to our data there is a substantial underreporting of ADRs leading to hospitalisation, even though the Dutch national Pharmacovigilance Centre is actively stimulating that clinicians should report such serious ADRs. On the other hand, the aim of a spontaneous reporting system is mainly to detect new signals (mostly type B reactions) and not to be overwhelmed by already well-known serious type A reactions regularly causing hospitalisations (f.e. gastrointestinal bleeding while using anticoagulants). Hence, we should place this underreporting into perspective.

A limitation of this study is that the proportion of ADR-related hospitalisations we found is probably an underestimation of the real situation. We have potential misclassification because not all ADRs may be recognized or mentioned in discharge letters and coded accordingly [22]. However, by using the above described coding system, the assessment of ADR-related hospitalisations is unbiased because the code clerks were not coding as part of a study (with a pre-defined hypothesis). As mentioned before, most other studies might come to higher estimations because they assess all admissions with the hypothesis that drugs may have played a role. This method is very sensitive to bias towards overestimation of ADR-related hospitalisations.

Another limitation of this study may be that the ADR-related hospitalisations also include admissions in which the ADR has occurred during the admission. Hence, cases are included in which the ADR has not been the reason for admission, but a complication during an admission. This makes a comparison with some other studies more difficult because several investigators define ADR-related hospitalisations only as admissions due to an ADR [3,4,6,8,13]. However, in a meta-analysis Lazarou et al. also combined admissions caused by an ADR and admissions during which an ADR occurred as ADR-related hospitalisations [2]. As they suggest,

we also think that admissions complicated by an ADR should be included as ADR-related, because an ADR may worsen or prolong a hospitalisation or even result in death. Furthermore, a limitation in our study is that hospitalisations coded with an E-code referring to a secondary diagnosis (n=6040) may have been admissions during which the ADR occurred or admissions caused by the ADR. We did not review all main diagnoses of these admissions, but in a sample review the main diagnosis was regularly similar to the secondary diagnosis that was coded with the E-code (i.e. E-code indirectly referring to main diagnosis), so in these cases we assumed that the ADR had been the reason for admission. Hence, we do not exactly know which hospitalisations in this 'secondary diagnosis group' had been caused, and which had been complicated by an ADR. We assumed that hospitalisations coded with an E-code referring to the main diagnosis (n=6209), were hospitalisations caused by the ADR.

In conclusion, as far as we know this is the first nationwide study of ADR-related hospitalisations occurring during one year in all hospitals in one country. Although our finding that 12,249 hospitalisations (1.83%) were ADR-related is considerable, these figures are lower than similar studies using chart review. Furthermore, we found that underreporting of serious ADRs leading to hospitalisation to our National Pharmacovigilance Centre is substantial.

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3.2

ADR-related hospitalisations: a population-based cohort study

Abstract

Background: The extent of Adverse Drug Reaction (ADR)-related hospitalisations has usually been assessed within hospitals. Because of the variability in results and methodology, it is difficult to extrapolate these results to a national level.
Objective: To evaluate the extent, characteristics and determinants of ADR-related hospitalisations on a population-based level in the Netherlands in 2003.
Methods: We performed a population-based cohort study to evaluate the extent of ADR-related hospitalisations that occurred in 2003 in the Netherlands. Data were retrieved from the Integrated Primary Care Information (IPCI) project, a general practice research database with data from computer-based patient records of a group of 150 general practitioners (GP) in the Netherlands. GP practices that had a recorded admission rate that corresponded with the national admission rate in the Netherlands were included in the study. Hospital discharge letters and patient records were reviewed to evaluate ADR-related hospitalisations. The prevalence of ADR-related hospitalisations per total admissions and the incidence per drug group use was evaluated. Also, determinants, avoidability and seriousness of the ADRs causing hospitalisation were assessed.
Results: In the eligible GP practices, 3515 hospital admissions were identified, 1277 were elective (day-admissions excluded) and 2238 were non-planned, acute admissions. Of the 2238 acute admissions, 115 were caused by an ADR, giving a prevalence of 5.1% (95% CI: 4.3%-6.1%). The prevalence of ADR-related acute admissions increased with age, up to 9.8% (95% CI: 7.9-12.2) for persons older than 75 years. The ADRs that were most frequently related to hospitalisations were gastro-intestinal bleeding caused by antithrombotics, bradycardia/ hypotension caused by cardiovascular drugs, and neutropenic fever caused by cytostatics. The incidence rate for ADR-related hospitalisations in relation to frequency of drug use was highest for antithrombotics and anti-infectives. Fatality as a direct consequence of the ADR-related admission was 0.35%. In elderly patients, 40% of the ADRs causing hospitalisation were judged to be avoidable.
Conclusions: The extent and potential avoidability of ADR-related hospitalisations is still substantial, especially in elderly patients. Measures need to be put into place to reduce the burden of ADRs.

Introduction

Hospitalisations caused or complicated by adverse drug reactions (ADRs) represent a substantial burden in health care [1]. Studies have estimated a wide variation in frequencies of ADR-related hospitalisations. Meta-analyses have calculated that hospitalisations attributed to adverse drug reactions (ADRs) account for between 2.4 % and 6.4 % of all hospital admissions in Western countries [2-5]. For the elderly this percentage has been estimated at 3.4 % to 16.6 % [4,6]. Recently, a large prospective in-hospital study estimated that 6.5% of all acute hospital admissions is related to ADRs in Great Britain [7]. So far, most studies evaluating ADR-related admissions were performed in the setting of one or a few hospitals. Moreover, many of these studies were performed in particular departments. Therefore, the results were difficult to extrapolate to other hospitals or to a national level, especially since results are often extrapolated to all (acute and planned) admissions whereas the ADR rate is mostly assessed in departments with a high rate of acute admissions. This might have led to an overestimation of the absolute problem.

To tackle these limitations, we performed a population-based cohort study using computer-based full medical patient records from general practitioners (GPs) to evaluate the extent of ADR-related hospitalisations that occurred in 2003 in the Netherlands, both in terms of the prevalence per total admissions and as incidence per drug use. Comparisons of the prevalence of ADR-related admissions as fraction of total admissions between countries are confounded by the extent of drug use. The incidence of ADR related hospitalisations during drug use is relevant to determine to identify which drugs are most harmful. It allows for a direct comparison between countries, and does not depend on differences or secular trends in hospitalisation [8]. The incidence has been estimated before by Hallas and Schneeweiss, and both of them noted that the sequence of 'harmful' drugs changes if incidence per drug use rather than prevalence per admission was calculated. However, both studies were not done with a primary study base [9,10].

To our knowledge, this is the first population-based study using GP practices with electronic patient records to define prevalence and incidence of ADR-related hospitalisations and to assess causality and avoidability.

Methods

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a general practice research database, containing data from computer-based medical

patient records of a group of 150 general practitioners (GPs) in the Netherlands. In the Dutch health care system, the GP has a pivotal role by acting as a gatekeeper for all medical care. Details of the database have been described elsewhere [11,12]. Briefly, the database contains the complete medical records of approximately 500,000 patients. The electronic records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses (using the International Classification for Primary Care [13] and free text) from GPs and specialists, referrals, laboratory findings, hospitalisations, and drug prescriptions. To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain paper-based records besides the electronic medical records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research in several studies that evaluated the quality of the available information [12]. The population in this database is representative of the Dutch population regarding age and sex. The Scientific and Ethical Advisory Board of the IPCI project approved this study.

Study population

We conducted a population-based cohort study in a dynamic population of patients. The study period started on January 1, 2003 and ended on December 31, 2003. The patients had to have been registered at the IPCI database for at least one year on January 1, 2003 (for valid history), and at GPs that 1) had been participating in the IPCI project for at least one year, 2) were still active at the moment that the study was performed and 3) had a recorded admission rate in line with the national admission rate in the Netherlands in 2001.

Assessment of ADRs

Of all eligible practices, the hospital admissions that occurred in 2003 were extracted from the electronic patient records. Research assistants visited the GP practices, copied the corresponding hospital discharge letters and made them anonymous. Subsequently, a team of 4 physicians with training in pharmacovigilance evaluated all discharge letters. If there was no discharge letter available, information about the admission was retrieved from the electronic patient records (one third of all admissions). If there was not enough information to classify the admission, it was excluded from the study. Also, planned admissions for one day were excluded because these mostly concern diagnostic procedures or planned small surgical activities.

Information on drug use at admission was obtained from both the discharge letter and from the electronic prescription records in the IPCI database.

The physicians evaluated all information together to assess ADR causality, using criteria developed by the World Health Organisation (WHO) [14]. Every discharge letter was independently evaluated by 2 physicians. Patients with either deliberate or unintentional overdose or those who relapsed because of non-compliance, were not judged as having an ADR. The admissions were categorized in line with the WHO definitions as: definitely related to an ADR (A), probably related to an ADR (B), possibly related to an ADR (C), unlikely or not related to any ADR (D), and not assessable (E) [14]. If hospitalisations were categorized as being caused or complicated by an ADR, all drug details were recorded plus clinical details of the reaction and the outcome. ADRs causing hospitalisation or complicating already hospitalised persons were categorized separately. The severity of the ADR was classified as life-threatening or fatal (contributed to or even caused death) in line with the definitions from Morimoto et al [15] . The avoidability of the ADRs was assessed by using definitions developed by Hallas et al. [16,17], as follows: 1) definitely avoidable – the ADR was due to a drug treatment procedure inconsistent with present day knowledge of good medical practice, 2) possibly avoidable – the ADR could have been avoided by an effort exceeding the obligatory demands of present day knowledge of good medical practice, 3) unavoidable – the ADR could not have been avoided by any reasonable means.

During consensus meetings, discharge letters were re-evaluated if there was a discrepancy in the validation of causality and/or avoidability between the 2 physicians who had initially evaluated these letters. In case of persistent disagreement, the judgment of a third physician was asked and taken as decisive.

Analysis

The prevalence of ADR-related admissions was expressed as the proportion of all acute hospitalisations in 2003. The incidence rate of ADR-related hospitalisations was calculated in relation to exposure to drugs classes (ADR rate per 100 person-years of drug use). The exposure duration for each drug was based on the prescribed number of units (tablets, capsules, etc.) divided by the prescribed daily number. Cytostatics were excluded from incidence rate calculations since these are mainly administered in hospital. To identify risk factors for hospitalisations attributed to an ADR, we performed univariate and multivariate unconditional logistic regression analyses, comparing characteristics of persons with ADR-related hospitalisations with characteristics of persons with non-ADR-related acute admissions. This was only done in persons with at least one drug prescription in the last 6 months. The following potential risk factors were analyzed: age, sex, number of drugs taken before admission, medical insurance and season of admission (trimester). The risks were expressed as odds ratios (OR) with 95% confidence limits. All analyses were

conducted using SPSS-PC version 11.0 (SPSS Inc., 1989 – 2001).

The inter-rater agreement for ADR causality prior to reaching consensus was assessed by kappa statistics.

To extrapolate results to the Netherlands, direct standardization for health insurance was used (age and gender distributions of the study population were representative of the Dutch population). Dutch reference data (acute hospitalisation rates by insurance) were obtained from the Dutch national registry for hospital admissions.

Results

The study population comprised 92,566 persons (66,645 person-years). **Table 1** shows the characteristics of the study population. The mean age was 38.4 years (SD=22.6). In this study population, 3,609 hospital admissions occurred in 2003. We excluded 94 (2.6%) of these admissions, because there was not enough information for evaluation. Of the 3,515 remaining hospital admissions, 1,277 were elective (day-admissions excluded) and 2,238 were non-planned, acute admissions (**table 2**). Of the acute admissions, 115 admissions were judged as ADR-related (definitely and probably related). The inter-rater agreement for causality assessment was good (92% agreement, kappa=0.67). The prevalence of hospitalisations caused by an ADR as a proportion of all acute hospitalisations in 2003 was 5.1% (95% CI: 4.3%-6.1%). Extrapolated to the Dutch population, the prevalence was 5.35% (95% CI: 5.30-5.41). The prevalence of ADR-related admissions in planned admissions was much lower (0.7%), resulting in an overall rate of 3.5% (95% CI: 2.7%-3.9%), if acute and planned admissions were taken as denominator (**table 2**).

The prevalence of ADR-related acute admissions increases with age, up to 9.8% (95% CI: 7.9-12.2) for persons older than 75 years (**table 3**). Increasing age was an independent risk factor for ADR-related hospitalisations (**table 4**). Most patients with ADR-related problems were admitted at the department of Internal Medicine (**table 5**).

The ADRs that were most frequently related to hospitalisations were gastro-intestinal bleeding caused by antithrombotics (n=19), bradycardia/hypotension caused by cardiovascular drugs (n=14), and neutropenic fever caused by cytostatics (n=11). The drug groups ranking as highest in the prevalence of drug-related hospitalisations were antithrombotics, cardiovascular drugs, antineoplastics/ immunosuppressives and CNS drugs (**table 6**). The incidence rate for ADR-related hospitalisations per drug group is also shown in table 6. Antithrombotics and anti-infectives were associated with the highest incidence rate.

Ninety-three patients died during an acute admission (93 / 2238 = 4.2%), of whom 7 as a direct consequence of the ADR (0.31%). Hence, 7 of the 115 ADR-related hospitalisations ended in death directly caused by the ADR (6.1%). Also, 7 ADRs were judged to be acute and life-threatening. Most of these 14 life-threatening and fatal ADRs concerned cerebrovascular bleeding caused by anticoagulant therapy.

Thirty-five of the 115 ADRs that caused hospitalisation (30.4%) were judged to be avoidable (table 3). Avoidability of the ADRs was highest in elderly patients (40.0%). The most important reasons for avoidability were: inappropriate drug or laboratory test monitoring (n=9), prescribing drug doses that were relatively too high (n=5), not giving gastroprotective therapy while indicated (n=5) and duplex anticoagulant therapy (vitamin K antagonists **and** aspirin, n=3).

Serious ADRs in hospital, occurred during 59 acute hospitalisations (2.7%). The percentage of ADRs causing admission and ADRs occurring in hospital together was 7.6% (n=171)

Table 1 Characteristics of study population

Characteristic	n	%
Population	92,566	
Sex		
male	44,938	48.5
female	47,628	51.5
Age		
≤16	18,776	20.3
17–55	51,499	55.6
56–75	16,526	17.9
>75	5,765	6.2
Health insurance		
sick fund	51,086	55.2
private	38,259	41.3
unknown	3,221	3.5

Table 2 ADR-related hospitalisations

Causality	Acute		Planned		Total	
	n	%	n	%	n	%
ADR						
A. definite	18	0.8	3	0.2	21	0.6
B. probable	97	4.3	4	0.3	101	2.9
C. possible	122	5.5	3	0.2	125	3.6
A+B	**115**	**5.1**	7	0.5	122	3.5
A+B+C	237	10.6	10	0.8	247	7.0
Total	**2238**	100.0	**1277**	100.0	**3515**	100.0

Table 3 ADR-related non-planned hospitalisations for different age categories and preventability

Age	n	ADR (A+B)	% (95% CI)	ADR preventability (%)
≤ 16	301	1	0.3 (0.1–1.4)	0
17–55	755	24	3.2 (2.3–4.4)	16.7 (7.7–32.4)
56–75	674	40	5.9 (4.6–7.6)	27.5 (17.6–40.3)
> 75	508	50	**9.8 (7.9–12.2)**	**40.0 (29.4–51.6)**
Total	2238	**115**	**5.1 (4.3–6.1)**	**30.4 (23.9–37.9)**

Table 4 Risk factors for ADR-related hospitalisations in drug users in 2003 (logistic regression)

	ADR	Univariate OR (95% CI)	Multivariate * OR (95% CI)
Sex			
Male	39	reference	
Female	57	1.3 (0.9 - 1.9)	
Age			
≤ 16	0	0.00	0.00
17–55	19	0.39 (0.23 - 0.69)	**0.45 (0.25 - 0.80)**
56–75	34	0.59 (0.37 - 0.94)	**0.60 (0.37 - 0.96)**
≥ 75	43	reference	reference
Number of drugs			
1 drug	8	reference	reference
2-3 drugs	21	1.70 (1.27 - 3.23)	1.27 (0.78 - 2.06)
4-7 drugs	29	1.81 (1.40 - 3.66)	1.11 (0.65 - 1.86)
> 7 drugs	38	3.02 (1.39–6.59)	1.99 (0.88–4.50)
Medical insurance			
Sick fund	63	reference	
Private	22	0.90 (0.55 - 1.49)	
Other	11	1.48 (0.76 - 2.89)	
Trimester			
Jan-March	20	reference	reference
April-June	23	1.23 (0.66 - 2.27)	1.20 (0.64 - 2.24)
July-Sept	30	1.62 (0.90 - 2.90)	1.57 (0.87 - 2.86)
Oct-Dec	23	1.14 (0.61 - 2.10)	1.17 (0.63 - 2.20)

* multivariate analysis including factors that are associated with ADR-related hospitalisation in univariate analysis ($p \leq 0.1$): age, number of drugs, trimester.

Table 5 Prevalence of ADR-related hospitalisations in departments with most acute admissions

Departments	Acute admissions	ADR-related	% (95% CI)
Internal medicine	462	61	13.2 (10.8–16.0)
Cardiology	337	15	4.5 (2.9–6.7)
Surgery	309	5	1.6 (0.8–3.3)
Pediatrics	228	1	0.4 (0.1–1.9)
Lung diseases	196	8	4.1 (2.3–7.1)
Neurology	180	12	6.7 (4.2–10.4)
Other	526	13	2.5 (1.6–3.9)

Table 6 Contribution of drug groups to prevalence and incidence of ADR-related admissions (2003)

Anatomical drug group (ATC) *	ADR #	% ADR	Use (PY)	ADR rate/100 PY	Preventable (%)
Gastrointestinal / metabolism	3	2.5	5236	0.1	33.3
antidiabetics	(2)				
Blood / bloodforming organs	40	**32.8**	3118	**1.3**	37.5
vit K antagonists	(20)				
aspirin	(17)				
Cardiovascular	32	**26.2**	11847	0.3	56.3
beta blockers	(14)				
diuretics	(8)				
anti-arrhythmics	(7)				
Dermatologics	1	0.8	1883	0.1	0.0
Genito-urinary / sex hormones	7	5.7	4059	0.2	14.3
anticonceptives / HRT ^					
Hormones	4	3.3	832	0.5	75.0
corticosteroids					
Anti-infectives	6	4.9	486	**1.2**	0.0
antibiotics	(5)				
Antineoplastics / immunosupp	22	**18.0**			4.5
Muscle-skeletal	9	7.4	1614	0.6	55.6
NSAIDs					
Nervous system	19	**15.6**	5790	0.3	36.8
opioids	(5)				
psycholeptics	(5)				
antidepressants	(3)				
Anti-parasitic	1	0.8	39	**2.6**	0.0
antimalarial					
Respiratory	1	0.8	3896	0.0	0.0
Sensory organs	0	0.0	445	0.0	0.0

* antineoplastics not included for incidence rate
# ADRs were counted more than once if several drugs were involved
^ HRT = hormone replacement therapy

Discussion

In this population-based cohort study, 5.1% of all acute hospitalisations in 2003 were definitely or probably attributed to ADRs. This is in line with previous studies that found similar prevalences [2-5,17]. The proportion of ADR-related hospitalisations increased with age from 0.3% in the age group below 16 years to 9.8% in the age group of 75 years and older, confirming that ADR-related admissions are more frequent in elderly persons. Age was an independent risk factor for ADR-related hospitalisations. In contrast to previous studies, the number of prescribed drugs was not a risk factor in our study, after adjusting for age (table 4). Another finding is that the prevalence of ADR-related hospitalisations varies widely between the different departments, with the highest prevalence at the department of Internal Medicine (table 5). This might partly explain the wide range of prevalences found in previous studies, because they were regularly performed in isolated departments [10,18-21].

The drugs most commonly involved in ADR-related hospitalisations were antithrombotics, cardiovascular drugs, antineoplastics and CNS drugs. Antithrombotics and anti-infectives had the highest incidence rate whereas cardiovascular drugs had a low incidence rate. The ranking was slightly different if based on the rate per total number of hospitalisations. This difference in ranking was brought to the public attention before by Hallas and Schneeweiss [9,10] and they underlined the fact that the incidence rate is essential to identify the most noxious drugs for users. Incidence rates are important to measure the effect of preventive measures and can be used to compare rates between different countries. The ranking based on prevalence as proportion of total admissions reflects which drug-ADR cases are most frequently seen. Although this is useful to estimate the public health burden and is easier to interpret, it depends heavily on changes in hospitalisation rates, which may vary over time and between countries [10].

A majority of the ADRs causing admission pertained to (gastrointestinal) bleeding while using anticoagulants. This has been found in other studies as well [6,10,17,22]. Fourteen of the 115 ADRs causing hospitalisation (12.2%) were acutely life-threatening (n=7) or even caused death (n=7), which is substantial. Most of these ADRs concerned cerebrovascular bleeding caused by anticoagulant therapy.

In previous studies evaluating avoidability [4,17,19,23-29], estimates ranged between 24% and 90%, depending on definitions used [30] and the population under study [4]. According to the criteria that were developed by Hallas et al, we estimated that approximately 30% of the ADRs leading to acute hospitalisation were definitely or possibly avoidable [31]. Avoidability was higher in the elderly (40% in persons aged > 75 years) than in younger persons (23% in patients aged 17 - 75 years). The two most important reasons for avoidability were: inappropriate drug or laboratory test monitoring, and prescribing drug doses that were relatively too

high for older patients. Several general preventive actions have been suggested to decrease the extent of (avoidable) drug-related hospitalisations. These suggestions vary from more attention for rational and appropriate prescribing by doctors, better doctor-doctor communication, better communication with patients and patient compliance, to automated drug prescribing and medication surveillance systems supporting doctors and pharmacists in good pharmacovigilance practice. We think that regular review of prescriptions in high risk groups (e.g. elderly patients), both by doctor and pharmacist, should be stimulated and should become common practice.

We have separately analyzed the prevalence of ADRs causing admission (5.1%) and the prevalence of ADRs complicating hospitalisations (2.7%). We also combined the 2 groups and obtained an overall ADR prevalence of 7.6% of all acute admissions. Similar results were found in a meta-analysis by Lazarou et al.[2] (4.7% resp. 2.1% resp. 6.7%), who suggest that admissions complicated by an ADR should also be judged as ADR-related, because an ADR may worsen or prolong a hospitalisation or even result in death.

The strength of this study is the population-based character with the possibility to study admission and drug use on a population level and independent of hospital or department. So far, most studies evaluating ADR-related admissions were performed in a local hospital setting. Even the widely cited document "To err is human" is based on results of only a small number of hospitals [1]. Therefore the results were difficult to extrapolate to other hospitals or to a national level [22,32]. Moreover, we had a longer study period of a year instead of short study periods of some weeks or months. Therefore, we were able to study potential season effects [33]. Last but not least, we were able to calculate the incidence of ADR-related hospitalisations [10], which gave us more insight into the relative contribution within drug classes to ADRs leading to admissions.

A limitation of this study is that we evaluated the hospitalisations retrospectively, and therefore depended on the information in the electronic medical record and discharge letters. For example, information on drug use at admission was not always complete and missed, for example, OTC drug use. Similar to other studies in this field evaluating charts or letters, another limitation is that of an admission which is attributed to an ADR is a clinical judgement of wich the quality may vary between individuals. To limit subjectivity, each admission was independently assessed by two physicians regarding causality and avoidability, and apparently there was a high degree of inter-observer agreement.

In conclusion, we were able to use very comprehensive patient information and drug data from a population-based database to study the extent of ADR-related hospitalisations. This type of study can help us to develop prevention measures in order to improve patient safety.

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4

Drug-induced atrial fibrillation

4.1

Drug-induced atrial fibrillation: a review

Abstract

Atrial fibrillation (AF) is the most common sustained rhythm disorder observed in clinical practice and predominantly associated with cardiovascular disorders such as coronary heart disease and hypertension. However, several classes of drugs may induce AF in patients without apparent heart disease or may precipitate the onset of AF in patients with preexisting heart disease. We reviewed the literature on drug-induced AF, using the PubMed/Medline and Micromedex database and lateral references. Successively, we discuss the potential role in the onset of AF of cardiovascular drugs, respiratory system drugs, cytostatics, central nervous system drugs, genito-urinary system drugs and some miscellaneous agents. Drug-induced AF may play a role in only a minority of the patients presenting with AF. Nevertheless, it is important to recognize drugs or other agents as a potential cause, especially in the elderly, because increasing age is associated with multiple drug use and a high incidence of AF. This may contribute to timely diagnosis and management of drug-induced AF.

Introduction

Atrial fibrillation (AF) is the most common sustained rhythm disorder observed in clinical practice. Its clinical importance is highlighted by a high prevalence and serious clinical consequences such as hemodynamic impairment and ischemic stroke. The prevalence increases with age, up to 4% in people over the age of 60 years and approximately 9% in people over the age of 80 years [1]. AF is associated with a 4- to 5-fold higher risk of ischemic stroke than the risk in the unaffected population [1-3]. Multicenter studies have addressed the fact that not only permanent AF, but also paroxysmal AF could predispose patients to systemic embolism [4-6].

Although AF can occur without detectable disease ("lone AF"), it is often associated with heart disease [7]. Increasing age, heart failure, smoking, diabetes mellitus, hypertension, male sex, left ventricular hypertrophy, myocardial infarction, valvular heart diseases, pulmonary diseases and hyperthyroidism are risk factors for AF [8]. Acute, temporary causes of AF include alcohol intake, stress, coffee in excess, surgery, peri-/myocarditis and pulmonary embolism [7].

Also drugs have been associated with the induction of AF in case reports and clinical trials. In this review, we will discuss these drugs and what is known about their potential mechanisms to induce AF. First, we will discuss shortly what is known about the etiology and mechanisms of AF to better understand the potential mechanisms of drugs to induce AF.

Etiology and mechanisms of AF

AF is associated with morphological changes in the atrial myocardium. This may result from AF itself or from other underlying disease processes, however it may also be general manifestations of the physiologic aging process. Changes in the autonomic innervation of the atrial myocardium and sinus and atrioventricular nodes are part of the normal aging process. Underlying disease may cause enlargement and structural changes of the atrial myocardium, vascular changes of sinus and atrioventricular nodes, acute and chronic inflammatory changes with necrosis, cellular infiltration, fatty metamorphosis, fibrosis and calcification. These changes in the atrial myocardium lead to the electrophysiological abnormalities that result in the mechanisms responsible for the occurrence of AF [9]. Electrophysiological effects in the atrium leading to AF can also be caused or triggered by physiologic processes such as adrenergic or vagal stimulation, metabolic or electrolyte disturbances, or by certain drugs or agents [10]. **Table 1** gives an overview of the most important conditions related to AF. As AF is often

associated with other supraventricular tachycardias (SVT), these conditions may also induce other SVT.

Review of the etiologic factors discussed above suggests that a common pathway exists among the many, diverse causes of AF. It is postulated that the onset of AF requires a trigger, such as an acute myocardial infarction or an intense neurological input to the atrium, or a drug, but that a substrate is also required for the onset and maintenance of the arrhythmia [11]. After cardiac surgery for instance, increasing age is the most powerful predictive factor for AF. Superimposed upon the age-related atrial changes are the triggers of adrenergic stimulation and perioperative pericarditis and/or atrial ischemia. The importance of adrenergic triggers is emphasized by the effect that beta blockade has in decreasing the occurrence of AF after a coronary artery bypass graft (CABG). That this trigger-substrate relation is a critical partnership in arrhythmia production is apparent from the fact that AF almost always resolves spontaneously within a few weeks after CABG [11]. Similarly, if a drug is stopped that triggers AF, the arrhythmia will often resolve.

Another postulated proarrhythmic mechanism [12] that fits the trigger-substrate relation is based on experiences in antiarrhythmic therapy and explained in **figure 1**. In reality, for arrhythmias due to re-entry, the mechanisms by which drugs cause arrhythmia are more complex than the model discussed in the legends of figure 1. We describe this model only for basic understanding.

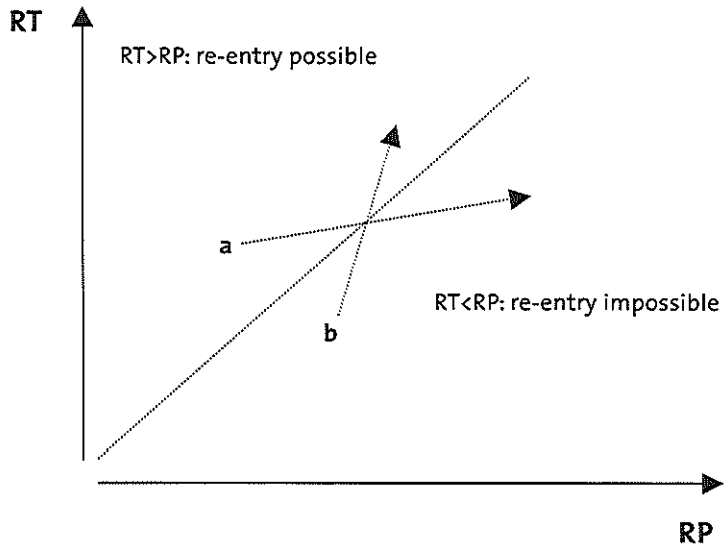
Methods

We reviewed the literature on drug-induced AF in English, from January 1974 to February 2003, using the PubMed/Medline and Micromedex (Drugdex) [13] database and lateral references. We used the key words 'atrial fibrillation' combined with 'drug-induced', 'chemically induced', 'associated with drug', 'as cause of drug' and 'as side effect'. Case reports with a very weak and uncertain association were excluded.

Review of drug-induced AF

It is of clinical importance to recognize drugs or other agents as a potential cause or trigger of AF, especially in the elderly, because increasing age is associated with multiple drug use and a high incidence of AF. Much has been published about severe proarrhythmic adverse effects of (antiarrhythmic) drugs, especially life-threatening drug-induced ventricular tachycardias and conduction disorders. It is not our aim to review these drug-induced arrhythmias, but to focus on drug-induced AF. AF is usually not an immediately life-threatening arrhythmia, but it

Figure 1 Drugs and re-entry tachycardia: pro- or antiarrhythmic effect



RT = Revolution Time
RP = Refractory Period

a = drug with a antiarrhythmic effect
b = drug with a proarrhythmic effect

Legends: Antiarrhythmic drugs have diverse electrophysiologic effects on conduction, refractoriness and automaticity in the heart. As an example we might consider the simplest form of AF due to re-entry around one or more obstacles (i.e. scars) that might be found in a patient with AF due to prior myocardial infarction. As a re-entry wavefront circulates around an obstacle it leaves in its wake a region of tissue that is refractory. In order for re-entry to be sustained around such an obstacle, the revolution time (RT) around the circuit must exceed the refractory period (RP), i.e., RT > RP. Otherwise, the wavefront would begin to encounter tissue that was still refractory, thereby preventing or extinguishing the re-entry. If RT < RP, re-entry is not possible, but when a (antiarrhythmic) drug slows conduction velocity more than it prolongs the refractory period, this drug could initiate re-entry (RT > RP) and the drug would be judged as proarrhythmic (**arrow b**). If a drug prolongs the refractory period to a greater degree than it slows conduction velocity, it will prevent re-entry and acts as antiarrhythmic (**arrow a**).

produces substantial discomfort and morbidity, is a major determinant of stroke [4-6] and may increase mortality, particularly in patients with structural heart disease [10]. Drugs may induce different types of SVT and possibly with a similar mechanism. In this review, however, we will focus on AF because this supraventricular arrhythmia is the commonest in clinical practice and known for its serious complications and potential permanent character.

Table 2 gives an overview of drugs that may induce AF and their potential mechanism, according to the literature. In this table can be seen that almost all drug-induced AF is reported to have the following main mechanisms: adrenergic or vagal stimulation, direct cardiotoxicity, changing atrial conduction, refractoriness or automaticity, coronary vasoconstriction/ischemia, and (local) electrolyte disturbances. A distinction has been made between agents reported in case reports to be associated with AF and agents mentioned in Micromedex to be able to induce AF. As far as we could retrieve, no studies have been published on drug-induced AF besides case reports.

Cardiovascular drugs

Cardiac stimulants

Several cardiac stimulants are known for their potential to induce SVT. This can be attributed to their adrenergic properties. AF has been reported with the use of dobutamine and arbutamine stress echocardiography [14,15]. Dopamine and dopexamine have been associated with AF when used for acute cardiac failure or hypotension after open heart surgery. Some cases converted spontaneously to sinus rhythm, others needed treatment [16,17]. In one case report, an older patient with left atrial enlargement developed sustained AF after dobutamine stress echocardiography [14].

Antiarrhythmics

It is well-known that antiarrhythmics can have proarrhythmic adverse effects, including AF and atrial flutter [12,18,19]. A possible mechanism is described above and is shown in figure 1. It is not surprising that antiarrhythmic drugs can cause arrhythmia in view of the diverse electrophysiologic effects on conduction, refractoriness and automaticity these agents have in the heart. In single cases it has been described that persons treated for AF by class IA and IC drugs, developed atrial flutter with 2:1 or 1:1 atrioventricular conduction [19,20]. We will focus now on the specific drugs associated with AF in the literature.

Adenosine can induce AF by the shortening of atrial action potential duration while it is used for terminating atrioventricular re-entry tachycardia. Most patients convert to sinus rhythm within a few minutes [21-23], but also a case has been

Table 1 Conditions related to Atrial Fibrillation

Cardiovascular conditions
Hypertension
Valvular disease
Cardiomyopathy
Coronary heart disease: *acute myocardial ischemia and infarction*
Peri-/myocarditis
Sick sinus syndrome
Cardiac surgery
Congenital heart disease
Noncardiovascular conditions
Pulmonary disease / embolism
Electrolyte abnormalities: *e.g. hypokalemia, hyperkalemia*
Adrenergic stimulation: *hyperthyroidism, pheochromocytoma, fever, stress, alcohol, caffeine, drugs, neurogenic*
Vagal stimulation: *neurogenic, drugs*
Idiopathic ("lone AF")

Table 2 Drugs* reported to potentially induce AF

Drug group	Drug	Mechanism
Cardiovascular		
Cardiac stimulants	Dopamine, dobutamine, dopexamine, arbutamine	Adrenergic stimulation
Vasodilatators [1]	Flosequinan, isosorbide mononitrate, losartan	Hypotension → adrenergic reflex?
Antiarrhythmics	Adenosine, verapamil, diltiazem, digoxin, atenolol	Changing atrial electrical properties
Cardiac ultrasound contrast agents [1]	Perflexane, perfluorobutane	Local stimulation?
Cholinergics	Acetylcholine	Vagal stimulation
Diuretics	thiazides	hypokalemia
Respiratory system		
Sympathicomimetic inhalants		
Alpha agonists	Pseudo-ephedrine	Adrenergic stimulation
Beta agonists	Albuterol #	Adrenergic stimulation
Xanthines	Aminophylline #	Adrenergic stimulation
Corticosteroids	Methylprednisolone (high dose)	Local potassium efflux

Table 2 (continued)

Drug group	Drug	Mechanism
Cytostatics	Gemcitabine #, melphalan, cisplatin #, docetaxel, 5-FU, etoposide, ifosfamide [1]	Several, cardiotoxicity
Cytokines and immunomodulators [1]	interferon gamma, interleukine-3, interleukine-6	Not reported
Photosensitizing agents [1]	Porfimer, verteporfin	Not reported
Central nervous system		
Cholinergics	Physostigmine, donepezil	Vagal stimulation
Anticholinergics	Atropine	Adrenergic stimulation
Dopamine-agonists	Apomorphine	Vagal activity
Antidepressants	Fluoxetine #	Serotonin?
	Tranylcypromine, trazodone	Not reported
Antipsychotics	Clozapine #	Not reported
Antimigraine	Sumatriptan #	Coronary spasm →ischemia
Anesthetics	Bupivacaine	Increasing cardiac automaticity
Genito-urinary system		
Drugs for erectile dysfunction	Sildenafil #	Hypotension → adrenergic reflex?
Drugs for premature labour	Hexoprenalin, terbutaline	Adrenergic stimulation
	Magnesium sulphate	Changing atrial conduction
Miscellaneous	Nicotine, anabolic steroids, fluorescein, etanercept, azathioprine	Several
Antithrombotic agents [1]	Anagrelide, clopidogrel	Not reported
Anti-emetica [1]	Alizapride, benzquinamide	Not reported
Miscellaneous [1]	Amifostine, disulfiram, etretinate, flupirtine, gallium nitrate, levocarnitine, nesiritide, niacin, zalcitabine, amphotericin B, pentagastrin, calcium	Not reported

*grouped by ATC code
[1] Micromedex (product information/clinical trials) [13]
causal relationship confirmed by recurrence of AF after rechallenge

documented that needed electrical cardioversion [24]. Case reports and experiments suggest that the calcium-channel blockers verapamil [25-27] and diltiazem [28] may aggravate or induce AF in susceptible patients. The mechanism is unknown. If AF develops in patients given verapamil or diltiazem for other indications, physicians should consider the drug as a possible cause of the arrhythmia. Digoxin can cause all sorts of arrhythmias and conduction disturbances, including AF [29]. Mostly this is a sign of intoxication. If digoxin is prescribed for heart failure and after a while AF and/or other arrhythmias develop, this may result from absolute or relative digoxin overdose. When digoxin is prescribed to convert AF to sinus rhythm and AF reoccurs, it may be difficult to assess its causation. In a study of the electrophysiological effects of atenolol, researchers made the observation that acute use of atenolol could facilitate the induction of AF in patients with a high incidence of paroxysmal AF and conduction abnormalities. The underlying mechanism is unclear [30].

Diuretics

Especially thiazide diuretics are known for hypokalemia as a potential side effect. Via this mechanism arrhythmia can be induced and also AF has been reported [31,32]. Therefore, regular electrolyte monitoring of patients using diuretics is essential and adding potassium-conserving diuretics can be helpful in patients susceptible to hypokalemia.

Cholinergics

Cholinergic drugs stimulate the vagal nervous system. Paroxysmal AF is a relatively common complication of coronary artery spasm provocation tests using intracoronary injection of acetylcholine, especially in patients with ischemic heart disease [33]. In a study of 740 patients, of the patients who developed AF during spasm provocation testing (n=116), 28.4% needed antiarrhythmic agents for conversion to sinus rhythm again. The potential mechanism is thought to be vagal stimulation by acetylcholine [33].

Some other cardiovascular drugs have been associated with AF in clinical trials, such as the vasodilatators flosequinan and isosorbide mononitrate and the echo contrast agents perflexane and perfluorobutane. Potential mechanisms were not reported [13,34].

Respiratory system drugs

Sympathicomimetic inhalants

Alpha and beta sympathicomimetic inhalants are prescribed to induce bronchodilatation in lung patients. They are known for their potential to cause cardiovascular adverse effects, such as sinus tachycardia and exacerbation of

existing arrhythmia. AF has been reported in infants less than one year of age after excessive therapeutic doses of pseudo-ephedrine (> 4 mg/kilo/day) [35]. Albuterol treatment using a spacer device was reported to induce AF with a positive rechallenge in a healthy young man. The authors think that the high dose administered through the spacer triggered the AF, because the man did not have complaints using a metered dose inhaler without spacer device [36].

Xanthines

The positive-inotropic, arrhythmogenic and chronotropic effects of xanthines are well-known [37-39]. AF associated with intravenous aminophylline has been reported in three patients without underlying cardiac disease. Rechallenge was positive in one patient [39]. Conversion to sinus rhythm occurred 9 to 14 hours after cessation of the drug in all three patients.

Corticosteroids

High doses of corticosteroids are standard treatment for a wide array of medical disorders. There are several case reports of AF following pulse methylprednisolone therapy: in 2 patients with multiple sclerosis [40,41], 2 children with nephrotic syndrome (one of them having systemic lupus erythematosus (SLE)) [42], in a man with SLE [43] and in a woman with rheumatoid arthritis [44]. Fujimoto et al postulated that methylprednisolone mediates potassium efflux via a direct effect on the cell membrane. Local potassium efflux may in turn influence arrhythmogenesis [45].

Cytostatics

The pathophysiology of chemically-induced arrhythmias by cytotoxic agents remains to be clarified. The hypotheses are multiple and include direct and indirect effects. The sinus node may be influenced by several stimuli, and a hyperstimulation of the parasympathic as well as of the sympathic system may cause abnormal function of the sinus node and abnormal intra-atrial or atrio-ventricular conduction [46,47]. Anthracyclines are associated with cardiac toxicity and brady- or tachy-arrhythmias. Cisplatin, 5-fluorouracil and etoposide have most frequently been associated with AF [47]. In cases of cisplatin-induced AF a positive rechallenge confirmed a causal relationship. The authors attributed this to direct myocardial toxicity [48]. Gemcitabine has been reported to induce AF with a positive rechallenge in a patient who had a history of a single brief paroxysm of AF [47]. The authors suggested a direct toxic effect of gemcitabine on the sinus node and/or the supraventricular conduction system. Ciotti et al describe another possible mechanism. They reported a case of severe cardio-pulmonary toxicity (ARDS and AF) after gemcitabine infusion and suggest an inflammatory pathogenetic mechanism

mediated by cytokine release resulting in myofibroblast proliferation and collagen deposits in lung and atrium [49].

AF after high-dose melphalan has been described in several cases without a history of structural heart disease or any other condition potentially causing AF such as fever, septicaemia or electrolyte imbalance [50]. A possible mechanism is not discussed. The authors speak of acute conduction cardiotoxicity.

Docetaxel-induced AF was recently described in a woman without any risk factors for AF [51]. The authors conclude that this is probably a rare adverse effect of docetaxel.

In all cases mentioned above, sinus rhythm was re-established by antiarrhythmic drug therapy.

Central nervous system drugs

(Anti)cholinergics

Cardiac dysrhythmias are among the major adverse reactions of the *anticholinergic* and vagal inhibitory agent atropine. Ophthalmic atropine eye drops after glaucoma surgery have been associated with AF. Two cases have been described and AF resolved after antiarrhythmic treatment [52].

The *cholinergic* agent physostigmine, a cholinesterase inhibitor and vagal stimulator, is commonly used to treat the central anticholinergic syndrome or post anaesthetic depression caused by a large number of drugs. One case report describes the occurrence of AF directly following the administration of physostigmine [53]. The mechanism is thought to be due to severe depression of both the SA and AV nodes due to vagal tone. This allows a latent re-entry focus to emerge within the atrial myocardium.

Also donepezil, a cholinesterase inhibitor used in Alzheimer's disease, has been associated with AF in clinical trials [13].

Dopamine-agonists

Apomorphine, a dopamine receptor agonist used in Parkinson's disease, has been associated with AF in a man without cardiovascular disease [54]. Five minutes after a subcutaneous bolus of apomorphine the man developed AF and was converted to sinus rhythm after medical treatment. Other possible causes for AF were excluded. Subcutaneous apomorphine injection has been reported to cause postural hypotension and vasovagal response in 10% of patients with parkinsonism [55]. The authors state that AF in this patient may have been induced by an imbalance of autonomic tone with increased vagal activity.

Antidepressants/antipsychotics

The selective serotonin reuptake inhibitor (SSRI) fluoxetine has been reported to provoke AF and a recurrence on rechallenge in an elderly woman with a history of mild stable angina, but no history of arrhythmia or myocardial infarction [56]. Because serotonin has an important role in the homeostatic control of the cardiovascular system, SSRIs can be expected to cause hemodynamic changes [57]. The authors state that in this woman with (mild) pre-existing heart disease, the cardiovascular effects of fluoxetine may have been able to trigger the onset of AF.

Similarly, the occurrence of AF following the use of the monoamine oxidase inhibitor (MAOI) tranylcypromine has been described in a young man without cardiovascular past but a history of alcohol abuse. A possible mechanism mentioned in this report is stimulation of cardiac catecholamine receptors by a decreased catabolism of tranylcypromine in an alcohol-damaged liver [58]. The atypical antidepressant trazodone has been associated with AF in a patient with underlying heart disease [59].

The atypical antipsychotic clozapine has been reported to induce AF with a positive rechallenge in a man without cardiovascular history. Antiarrhythmic therapy was needed to convert to sinus rhythm again. A potential mechanism is not described. Other side effects of clozapine such as orthostatic hypotension, sinus tachycardia, heart failure and ECG changes are well known [60].

Antimigraine drugs

The antimigraine drug sumatriptan, a serotonin-1 agonist, has frequently been associated with chest pain and myocardial infarction [61-64]. This is presumed to be due to vasoconstriction of the coronary arteries. AF associated with sumatriptan is uncommon, but several cases have been reported, also with positive rechallenge [65]. The authors suggest that myocardial ischemia secondary to coronary vasospasms could be a trigger for AF. This mechanism is also postulated by Hung et al. [66]. Hung described a patient who regularly developed paroxysmal AF after early morning chest tightness. Medical history only mentioned well controlled hypertension. Coronary artery spasm provocation with methylergonovine was performed to test whether AF was the result of coronary artery spasm. The patient indeed developed AF during the provocation test. Sueda et al. reported that paroxysmal AF often occurred during spasm provocation tests with acetylcholine, especially in patients with ischemic heart disease. They suggested that vagal stimulation by acetylcholine triggered the onset of AF in susceptible patients [33]. However, the mechanism may also be myocardial ischemia secondary to coronary vasospasms, as described above.

Anesthetics

AF has been described during epidural anaesthesia with bupivacaine in a man with a history of stable angina pectoris but no arrhythmias [67]. The AF persisted despite treatment during the period of epidural blockade. Only after the anaesthesia was terminated, reversion to sinus rhythm occurred. The reporters suggest that bupivacaine inhibits the Na^+K^+ pump, hence reducing the resting cell membrane potential. This may increase cardiac automaticity especially in cardiac fibres already partially depolarized because of ischemic heart disease. The authors postulate that bupivacaine acted as a trigger for the onset of AF.

Genito-urinary system

Drugs for erectile dysfunction

Three case reports describe AF after taking sildenafil [68-70]. One in a healthy young man, who interrupted coitus because he felt light-headed and had palpitations which were followed by a brief syncopal episode [68]. He failed chemical conversion twice, but converted spontaneously to sinus rhythm two days later. It was suggested that sildenafil caused profound hypotension leading to syncope and reflex tachycardia via catecholamine excess. Another report describes a 50-year-old man with a hypertrophic cardiomyopathy who developed AF with dizziness and converted to sinus rhythm after medical treatment [70]. This man had a positive rechallenge several weeks later. A third report describes AF and hypotension in a man one hour after taking sildenafil [69]. He was diagnosed with a Wolff-Parkinson-White syndrome 12 years before. Four hours later he returned to sinus rhythm spontaneously. The authors speculate that AF was caused by increased sympathetic activity due to hypotension, which may be provoked by sildenafil.

Drugs for premature labour

Hexoprenaline is a beta-adrenergic agonist used for treatment of premature labour. AF has been reported in a young woman without cardiovascular disease during intravenous treatment with hexoprenaline [71]. Eight hours after cessation of the drug the heart rate spontaneously converted to sinus rhythm. The authors state that it is reasonable to expect that arrhythmias and other adrenergic adverse effects may occasionally be produced by this drug.

Oral use of terbutaline, also a beta-sympathomimetic drug, has been associated with AF in a healthy pregnant woman with preterm labour. After several attempts of medical antiarrhythmic treatment, she converted to sinus rhythm [72]. Magnesium sulfate has widespread use in pregnancy both in pre-eclampsia as an anticonvulsant drug and as a tocolytic drug. In a woman with pre-eclampsia and without history of cardiac disease, AF occurred during treatment with magnesium

sulphate and resolved spontaneously after discontinuation. This drug has antiarrhythmic properties by slowing the conduction in the atrioventricular node, but in this case probably induced AF. Serum levels were within therapeutic range [73].

Miscellaneous

Apart from the categories of drugs discussed in the previous paragraphs, various other agents have been associated with the occurrence of AF.

Nicotine is widely used as an aid to smoking withdrawal. There are several reports of nicotine induced AF [74-76]. Nicotine overdose taken as chewing gum or nasal inhalator can result in increased heart rate and can be a potential danger for developing AF, even in individuals without a history of cardiac disease. AF has also been described in a patient with mild cardiovascular disease taking the usual amount of nicotine gum [75].

High doses of anabolic steroids have been reported in association with AF [77], as with hypertension, ischemic heart disease, hypertrophic cardiomyopathy and sudden death. A healthy 22-year-old male bodybuilder developed symptomatic AF after taking high doses anabolic steroids for 5 weeks. An echocardiogram showed some left atrial hypertrophy and septal hypokinesis, but it remained unclear if this was caused by the steroids. He was hospitalised and converted spontaneously to SR after 2 days of stopping the intake of the steroids. AF did not reoccur after discharge.

Intravenous fluorescein has been associated with AF. A 56-year old man with negative cardiac history developed AF just after administration of fluorescein during ankle surgery. Cardioversion was eventually required to restore sinus rhythm. Adverse reactions to fluorescein are not rare and frequently take the form of an allergic reaction. The authors suggest that non-specific histamine releasing mechanisms can explain the onset of AF in this patient, because histamine has long been known to have effects on cardiac rhythm through several different mechanisms [78,79].

A patient without risk factors for AF has been reported developing AF after a combination of etanercept and methotrexate for rheumatoid arthritis [80]. The authors speculate that blocking TNF-alpha receptors with etanercept could cause increased intracellular calcium in the myocyte and perhaps make the myocyte more excitable.

Azathioprine, an immunosuppressive agent used in severe psoriasis, has been associated with AF, but one of the reported patients abused alcohol and developed high fever while using azathioprine. Such factors could also have been responsible for triggering AF [81,82]. The other reported, also speculative, case had no comorbidity and developed AF after four weeks of use. Other known possible causes for AF were excluded and AF persisted for at least one year.

Discussion

There are different pathways to the initiation of AF. Therefore it is not surprising that several categories of drugs with different mechanisms of action have been associated with the onset of AF. Evidence associating drugs with AF is scanty and largely based on individual case histories. Even in cases in which a close temporal relationship between drug intake and initiation of AF exists, this may be a chance finding or be caused by the underlying condition ("confounding by indication"). Nevertheless, in several cases reoccurrence of AF after rechallenge confirmed a causal relationship. Such proof is not very common, however, as rechallenge is only ethical when it concerns a drug which is essential for the treatment of the patient and when a causal role of the drug is still inconclusive. However, if other known possible causes for AF are excluded and a plausible mechanism is available, the likelihood of a causal relationship increases. Pathophysiologically, drugs that increase or decrease adrenergic or vagal activity, such as sympathicomimetics, parasympathicomimetics and their inhibitors, may be able to cause AF, especially in susceptible patients with a history of cardiovascular disease (disease is the substrate, drug is the trigger), but also in 'healthy' patients. These drugs represent a substantial part of cardiovascular, respiratory and central nervous system medications. Antiarrhythmic drugs can paradoxically induce dysrhythmias as well, including AF and atrial flutter, by influencing the electrical properties of the atrial myocardium. Coronary spasm induced by certain drugs, such as acetylcholine and sumatriptan, may cause AF via myocardial ischemia. Cytostatics seem to have a more direct toxic effect on the heart, potentially initiating AF. The underlying disease and drug together can play an important role in the induction of AF (substrate-trigger relation), especially in thorax or lung carcinoma.

Most of the time it is not difficult to diagnose drug-induced AF because there is a direct time relationship between the administration of the drug and the onset of AF. However, if a patient presents with new-onset AF, it should be routine to review, besides the medical history, what medication or other agents the patient is using that may be able to induce AF. If there is suspected drug-induced AF after exclusion of other causes, the suspected drug/agent should be stopped and AF treated if it persists after discontinuation. It may be important to have an idea about the underlying cause or mechanism, and if overdose is not the issue, it may be advisable to find an alternative drug or treatment for the condition the drug was given for. If the drug is necessary for the patient, it may be advised to restart the drug in a lower dose and monitor the patient adequately for recurrence of AF. If AF recurs, continuous treatment to control AF is needed.

Much has been published, including observational studies, about severe

pro-arrhythmic side effects of drugs, especially life-threatening drug-induced ventricular arrhythmias frequently associated with QT interval prolongation. Epidemiological studies to quantify the relation between certain drugs and AF have not been performed yet, although AF is a very common arrhythmia with substantial morbidity and potentially serious complications. We think more research is needed, such as experimental and observational studies, to get more insight into the effect of drugs on the development of AF.

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4.2

Corticosteroids and the risk of atrial fibrillation

Abstract

Background: High dose (pulse) corticosteroid therapy has been associated with the development of atrial fibrillation. This association, however, is mainly based on case reports.
Objective: To test the hypothesis that high dose corticosteroid exposure increases the risk of new-onset atrial fibrillation.
Methods: We performed a nested case-control study within the Rotterdam Study, a population-based cohort study among 7983 older adults. Cases were defined as persons with incident atrial fibrillation between July 1st, 1991 and January 1st, 2000. Their date of diagnosis was defined as the index date. All non-cases within the Rotterdam Study who were alive and eligible on this index date, were used as controls. Subsequently, we compared the proportion of cases and controls that received a corticosteroid prescription within one month preceding the index date. Corticosteroid exposure was categorized into 'high dose' exposure (oral or parenteral steroid at a daily dosage ≥ 7.5 mg of prednisone equivalents) and 'low-intermediate dose' exposure (< 7.5 mg of prednisone equivalents or inhaled corticosteroids).
Results: The risk of new-onset atrial fibrillation was significantly higher for persons who received a corticosteroid prescription within one month before the index date than for those without (OR = 3.75 [95% CI: 2.38-5.87]). However, only 'high dose' corticosteroid use was associated with an increased risk (OR = 6.07 [95% CI: 3.90-9.42]), whereas 'low-intermediate dose' use was not (OR = 1.42 [95% CI: 0.72-2.82]). The association of atrial fibrillation with high dose corticosteroid use was largely independent of the indication for corticosteroid therapy, since the risk of new-onset atrial fibrillation was not only increased in patients with asthma or COPD (OR = 4.02 [95% CI: 2.07-7.81]) but also in patients with rheumatic, allergic or malignant hematologic diseases (OR = 7.90 [95% CI: 4.47-13.98]).
Conclusions: Our findings strongly suggest that patients receiving high dose corticosteroid therapy are at increased risk of developing atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common sustained rhythm disorder observed in clinical practice. Its clinical importance is highlighted by a high prevalence, and serious clinical consequences such as hemodynamic impairment and ischemic stroke. The prevalence increases with age and is up to 4% in people over the age of 60 years, and approximately 9% in people over the age of 80 years [1]. AF is associated with a 4- to 5-fold increased risk of ischemic stroke [1-3] and not only permanent AF, but also paroxysmal AF may predispose patients to systemic embolism [4-6]. Although AF can occur without detectable disease ("lone AF"), it is often associated with heart disease [7]. Increasing age, heart failure, smoking, diabetes mellitus, hypertension, male sex, left ventricular hypertrophy, myocardial infarction, valvular heart diseases, pulmonary diseases, and hyperthyroidism are risk factors for AF [8]. Acute, temporary causes of AF include alcohol intake, excessive coffee intake, surgery, pericarditis, myocarditis and pulmonary embolism [7].

Also drugs have been associated with the onset of AF, but knowledge about the role of drugs in the development of AF is scarce [9]. High dose corticosteroid therapy has been associated with the development of AF, but this is mainly based on case reports [10-14]. It is postulated that high dose corticosteroids mediate potassium efflux via a direct effect on the cell membrane, which may induce arrhythmogenesis [15]. To our knowledge, epidemiological studies investigating the research hypothesis that corticosteroid therapy may induce AF, have never been performed.

Therefore, we performed a nested case-control study to test the hypothesis that corticosteroid use increases the risk of new-onset AF.

Methods

Setting

This study was conducted as part of the Rotterdam Study, a prospective population-based cohort study on the occurrence and determinants of disease and disability in elderly persons [16]. In 1990, all inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, who were 55 years of age or older and who had lived in the district for at least 1 year were invited to participate in the study. Of the 10275 eligible persons, 7983 (78%) participated. Participants gave informed consent and permission to retrieve information from medical records. At baseline, trained interviewers administered an extensive questionnaire during a home interview covering socio-economic background and medical history, among other topics. During subsequent

visits to the study center, additional interviewing, laboratory assessments, and clinical examinations were performed, including recording of electrocardiograms (ECG). Follow-up examinations were carried out periodically (every 4 to 5 years). All drug prescriptions dispensed to participants by automated pharmacies are routinely stored in a database. Information on vital status is obtained at regular time intervals from the municipal authorities in Rotterdam. The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study.

For the present study, all participants were followed from baseline until they had incident AF, died, or reached the end of the study period at 1 January 2000, whichever came first. Because we had pharmacy dispensing records as of 1 January 1991, and included a medication history of at least 6 months, all cases of incident AF before 1 July 1991 were excluded from the analyses.

Cases and controls

Three methods were used to assess new cases of atrial fibrillation: (1) At baseline and during follow-up examinations, electrocardiograms (ECG) were recorded at the research center with an ACTA electrocardiograph (ESaOte; Florence; Italy), stored digitally, and were subsequently analyzed by the Modular ECG Analysis System (MEANS) [17-19]. The reported sensitivity and specificity of the MEANS program in coding arrhythmia's is high (96.6% and 99.5% respectively)[19]. To verify the diagnosis of AF, all ECGs with a diagnosis of AF or atrial flutter or any other rhythm disorder were recoded independently by two physicians who were blinded to the MEANS diagnosis. The judgment of a cardiologist was asked and taken as decisive in case of persistent disagreement. (2) General practitioners (GPs) participating in the Rotterdam Study send computerized information on selected diseases to the researchers of the Rotterdam Study on a weekly basis. Specially trained follow-up assistants verified this information using GP records and hospital discharge letters. A senior physician examined all information and coded the events according to the International Classification of Diseases, 10th revision (code I48). (3) Data on AF were acquired by linkage to a national registry of all hospital discharge diagnoses in the Netherlands. All diagnoses of AF were subsequently verified.

Those who developed AF during a serious disease resulting in death very shortly after the detection of AF, while AF was not the cause of the serious disease, were not considered as having AF. Furthermore, AF during myocardial infarction and during cardiac operative procedures were not included as new cases if the condition disappeared in a few days and did not reappear. Persons with prior or prevalent AF at baseline detected by any case identification method were excluded. Also, persons with incident AF discovered coincidentally during one of the follow-up

examinations were excluded from the current study if the date of onset of AF was unknown. For all cases of newly identified AF during follow-up, the earliest date of diagnosis (from GP records, ECG or hospitalisation) was taken as the index date.

To each case, we matched all persons in the cohort who were alive and at risk for new-onset AF on the index date of the corresponding case. The controls received the index date of the case to which they were matched.

Exposure definition

In the research area, there are 7 fully computerized pharmacies that are linked to 1 network. During the study, all participants filled 98% of their prescriptions in 1 of these 7 pharmacies. Data on all dispensed drugs since 1 January 1991 are available in computerized format on a day-to-day basis. The data include the date of prescribing, the total amount of drug units per prescription, the prescribed daily number of units and product name.

Persons who received a corticosteroid prescription for oral, rectal, parenteral or inhaled use within one month before the index date were defined as exposed, all others were considered as non-exposed. Corticosteroid exposure was categorized as 'high dose' exposure (oral, parenteral or rectal steroids with daily dosage equivalent to ≥ 7.5 mg prednisone) and 'low-intermediate dose' exposure (oral, parenteral or rectal steroids with daily dosages equivalent to < 7.5 mg prednisone, or inhaled corticosteroids) [20]. Exposed persons were further categorized as new users (first prescription) and prior users, to compare the risk for developing AF between starters and persons who had used steroids before.

To study potential confounding or effect modification by asthma/COPD status, stratified analyses were conducted for presence or absence of asthma/COPD, as proxied by the dispensing of more than 2 bronchodilator prescriptions prior to the index date.

Cofactors

The following patient characteristics were individually assessed as potential confounders: age, sex, hypertension, heart failure, myocardial infarction, diabetes mellitus, body mass index (kg/m2), smoking (classified as current/former/never), total serum cholesterol (mmol/l), hyperthyroidism and prevalence of left ventricular hypertrophy on the ECG. Hypertension was defined as systolic blood pressure > 160 mm Hg and diastolic blood pressure > 100 mm Hg, or use of any antihypertensive drug. Criteria for prevalent and incident myocardial infarction and heart failure have been described in detail earlier [21-23]. Diabetes mellitus was defined as a random or post load glucose level >=11.1 mmol/l and/or the use of blood glucose lowering medication prior to the index date.

Data on use of other medications within one month before the index date, such as antihypertensives (vasodilators, diuretics, beta blockers, calcium antagonists and ACE inhibitors) and anti-asthmatics (other than inhaled corticosteroids) was obtained from pharmacy records and analyzed as a potential confounder.

Statistical analysis

Conditional logistic regression analyses were performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between the use of corticosteroids and AF. To adjust for potential confounders, cofactors associated with the occurrence of AF were included one-by-one in the age- and sex-adjusted model. Cofactors that changed the point estimate by more than 5% were maintained in the multivariate model. All statistical analyses were performed using SPSS-PC version 11.0 (SPSS Inc., 1989 – 2001). Stratified analyses were performed for subjects on corticosteroids for asthma/COPD and for subjects with other indications.

Results

During the follow-up period, we identified 435 cases of new-onset AF after July 1st, 1991. After exclusion of 50 cases of AF in which the date of onset was unknown, 385 cases were eligible for this study. **Table 1** shows the baseline characteristics for cases and controls. Cases were on average older than controls, more often male, and had on average a higher body mass index. Also, cases were more likely to have hypertension, prior myocardial infarction, heart failure, diabetes mellitus, left ventricular hypertrophy on ECG and were more likely to be current or former smoker at baseline, after adjustment for age and sex.

The risk of new-onset AF was significantly higher for corticosteroid users than for those who were unexposed (OR = 3.75 [95% CI: 2.38-5.87]). The risk of new-onset AF was dose-dependent as exposure to low or intermediate daily doses was associated with a non-significant risk increase (OR = 1.42 [95% CI: 0.72-2.82]), while high dose exposure was associated with a more than 6-fold increased risk (OR = 6.07 [95% CI: 3.90-9.42] (**table 2**). Newly exposed persons had a somewhat higher risk for AF than persons who had received corticosteroids before (OR = 6.0 [95% CI: 2.2-16.2] versus OR = 3.49 [95% CI: 2.17-5.62]), but this difference was not statistically significant (**table 2**).

The association of AF with high dose corticosteroid use was largely independent of the indication for corticosteroid therapy, since the risk of new-onset AF was significantly higher both in patients with asthma or COPD

(OR = 4.02 [95% CI: 2.07-7.81]) as well as in patients with rheumatic, allergic or malignant hematologic diseases (OR = 7.90 [95% CI: 4.47-13.98] **table 3**).

Table 1 Baseline characteristics of the study population

Characteristic	Cases (n = 385)	Controls (n = 6364)	OR * (95% CI)
Sex			
Men	174 (45%)	2554 (40%)	1.00 (reference)
Women	211 (55%)	3810 (60%)	0.64 (0.52-0.79)
Age, year #	72.9 ± 7.8	68.8 ± 8.9	1.08 (1.06-1.09)
Hypertension	175 (46%)	2105 (33%)	1.55 (1.27-1.91)
Heart failure	23 (6%)	153 (2%)	2.06 (1.34-3.17)
Prior myocardial infarction	90 (23%)	741 (12%)	2.14 (1.68-2.72)
Diabetes mellitus	65 (17%)	618 (10%)	1.76 (1.35-2.30)
Smoking			
Current	84 (22%)	1452 (23%)	1.43 (1.05-1.96)
Former	175 (46%)	2611 (41%)	1.39 (1.06-1.89)
Never	122 (32%)	2213 (35%)	1.00 (reference)
Left ventricular hypertrophy	29 (8%)	248 (4%)	1.88 (1.28-2.76)
Hyperthyroidism	11 (3%)	243 (4%)	0.78 (0.43-1.43)
BMI, kg/m2 #	27.0 ± 3.8	26.3 ± 3.7	1.05 (1.03-1.08)
Total cholesterol, mmol/l #	6.5 ± 1.2	6.6 ± 1.2	0.97 (0.89-1.06)

* Odds Ratio for new-onset AF, age and sex adjusted, # mean ± SD

Table 2 Association between new-onset atrial fibrillation and corticosteroid therapy

Corticosteroid prescription #	Cases (n = 385)	OR* (95% CI)	OR** (95% CI)
No	342	reference	reference
Yes	43	4.08 (2.97–5.61)	**3.75 (2.38–5.87)**
Daily dose			
Low-intermediate dose	14	1.96 (1.15–3.34)	1.42 (0.72–2.82)
High dose	29	8.58 (5.86–12.55)	**6.07 (3.90–9.42)**
User status			
First prescription	4	6.2 (2.3–16.5)	**6.0 (2.2–16.2)**
≥ 1 prescriptions before	39	3.97 (2.85–5.53)	**3.49 (2.17–5.62)**

in 30 days before index date
* adjusted for age and sex
** adjusted for age, sex, myocardial infarction, heart failure, body mass index, use of antihypertensives and use of bronchodilators in month before index date

Table 3 New-onset atrial fibrillation and corticosteroid therapy in different patient groups

Corticosteroid prescription #	Cases (n=385)	OR* (95% CI)	OR** (95% CI)
In asthma/COPD patients			
No corticosteroids	43	reference	reference
Low-intermediate dose	13	1.46 (0.78–2.76)	1.40 (0.73–2.70)
High dose corticosteroids	13	4.71 (2.51–8.81)	**4.02 (2.07–7.81)**
In patients with other diseases			
No corticosteroids	299	reference	reference
Low-intermediate dose	1	0.78 (0.11–5.55)	0.57 (0.08–4.24)
High dose corticosteroids	16 ^	10.78 (6.50–17.83)	**7.90 (4.47–13.98)**

in 30 days before index date
* adjusted for age and sex
** adjusted for age, sex, myocardial infarction, heart failure, body mass index, user status, use of antihypertensives in month before index date
^ steroid indication: polymyalgia rheumatica, rheumatoid arthritis, (acute) bronchitis, allergic skin reaction, multiple myeloma and non-Hodgkin's lymphoma

Discussion

This population-based study shows that current use of high dose corticosteroids is associated with an increased risk of new-onset AF. This association was found in asthma/COPD patients as well as in patients without asthma/COPD.

Wei et al. recently reported an increased risk of hospitalisation for cardiovascular disease (myocardial infarction, heart failure, ischemic stroke) in high dose corticosteroid users [20]. The researchers explained this finding among others by the (long-term) cardiovascular adverse effects of corticosteroids, such as hypertension, diabetes mellitus and obesity, which are independent risk factors for cardiovascular disease. In our study, the finding of an increased risk of AF, especially in new, high dose users suggests that there is also a potential direct arrhythmogenic effect. Arrhythmogenic effects (including life-threatening arrhythmias) following corticosteroid pulse therapy have been described before in case reports [10-14, 24-26] and in a recent case-control study [27]. Several mechanisms are likely to be involved in the development of AF in patients treated with (high dose) corticosteroids. Firstly, it has been postulated that high dose corticosteroids mediate (local) potassium efflux via a direct effect on the cell membrane, which may induce arrhythmogenesis [15]. Secondly, high doses of glucocorticosteroids can have mineralocorticosteroid effects, such as retention of sodium and fluid, which may cause hypertension, left atrial enlargement and congestive heart failure – all known risk factors for AF [28]. Other proposed potential mechanisms are development of late potentials, profound peripheral vasodilatation and anaphylactic reactions [29,30]. However, there is yet no conclusive evidence for any of these mechanisms.

In a recent case-control study, Huerta et al.[27] reported a positive association between short-term oral corticosteroid therapy and cardiac arrhythmias (including AF) in persons with COPD or asthma. The association was not investigated in persons without COPD or asthma. Consequently, confounding by indication could not be excluded. However, in our study we found an association in asthma/COPD patients as well as in patients without asthma/COPD.

The fact that we only found an association in patients receiving high dose steroid exposure is in line with the study by Huerta et al.[27], who also did not find an association with the use of inhaled corticosteroids (low dose steroid exposure) and cardiac arrhythmias. We found an increased risk for AF as well in recent, new corticosteroid users as in persons who used corticosteroids before, supporting the hypothesis that corticosteroids have a potential direct arrhythmogenic effect (**table 2**). That new corticosteroid users even seem to have a higher risk to develop AF compared to persons who also used corticosteroids before, could be explained by the fact that all new users who developed AF (n=4) concerned high dose users. The more chronic users who developed AF (n=39) concerned a mix of high dose

(n=25) and low-intermediate dose users (n=14). The higher relative risk in patients with rheumatic, allergic or malignant hematologic diseases than in patients with asthma or COPD (**table 3**) could be explained by the fact that the prescribed steroid doses are usually highest in the first patient group.

Several aspects of validity need to be discussed. Selection bias is unlikely because cases and controls were derived from a prospective population-based cohort study, and controls came from the same study base as cases. Information bias is unlikely as data on drug use were prospectively gathered. As corticosteroids are only available on prescription, pharmacy records provide complete coverage. Compliance to systemic corticosteroids is usually good because such patients are often seriously ill. Misclassification of the diagnosis of AF is unlikely and would be random, because the outcome was assessed independently of the exposure. Misclassification of the index date is possible, because the date of diagnosis is not always the same as the date of onset of AF. To decrease the degree of misclassification of index date, we excluded AF cases with an unknown date of onset. In our study, it is unlikely that confounding explains our results, because we were able to adjust for many important potential confounders. Moreover, confounding by indication is not likely to explain the association. We were able to study the association both in persons with asthma or COPD, and in those with other indications for corticosteroid therapy. This makes it highly unlikely that the indications asthma or COPD, which are independent risk factors for AF [8,31], confounded our results. The patients who received high dose corticosteroids for other indications than asthma or COPD and who developed AF (n=16), received corticosteroid therapy for various indications: polymyalgia rheumatica (n=6), rheumatoid arthritis (n=1), (acute) bronchitis (n=4), allergic skin reaction (n=1), as concomitant therapy for multiple myeloma (n=1) and non-Hodgkin's lymphoma (n=1), and unknown indications (n=2). As these indications are so heterogeneous, we do not expect that these diseases confounded our results. Moreover, the strong risk increases make residual confounding unlikely.

In conclusion, our findings suggest that patients receiving high dose corticosteroid therapy (including recent starters) are at increased risk of developing AF. Therefore, careful monitoring of these patients by clinical examination and by performing an ECG before and after high dose (pulse) therapy, could increase the chance to diagnose and treat this serious arrhythmia as early as possible. As persons who develop AF are at increased risk of serious cardiovascular complications such as heart failure and ischemic stroke, and have a chance to develop chronic AF, early detection of AF is essential.

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5

General discussion

The main objective of this thesis was to examine the quality of prescribing and clinically important adverse consequences of pharmacotherapy in the elderly. Pharmacotherapy in the elderly is an important aspect of medical care [1]. It is obvious that drugs may have beneficial effects in the elderly population, also in the very old. For example, it has been demonstrated that the use of statins should not be limited to people younger than 70 years, as statins can reduce the risk of myocardial infarction even in the very old [2]. Also, the benefits of oral anticoagulant therapy in older patients with atrial fibrillation have been well established [3]. However, aspects of the aging process that occur in healthy elderly and that are considerably magnified in vulnerable elderly patients increase their risk for adverse drug reactions (ADRs) [4]. These include impaired renal function in clearing drugs that are primarily excreted by the kidney; reduction in hepatic flow, liver size and phase I degradative metabolic processes; increased body fat which increases the volume of distribution for lipid-soluble drugs and prolongs their half-life; and aging-induced changes in receptor sensitivity, which can further complicate the prediction and assessment of drug effects. Furthermore, increasing co-morbidity and multiple drug use increase the risk of ADRs [5]. ADRs can result in significant morbidity, hospitalisations or even death, and account for a substantial increase in health care costs [6,7]. An important meta-analysis estimated that annually more than 2 million hospitalised patients have severe ADRs in the United States, even when drugs are appropriately prescribed and administered, and that ADRs are estimated to be the fifth most common cause of death among hospitalised patients in the United States in 1994 [8]. Several reports and policy initiatives have emphasized greater efforts to reduce the incidence of adverse events in medical care [9-11]. In 2000, the Institute of Medicine in the USA reported that as many as 98,000 people die annually as the result of medical errors in the USA and called for an effort to make health care safer. This internationally known report 'To err is human: building a safer health care system' [9], launched a great lobby to improve patient safety and was the basis for many policy and health care initiatives in this field. Patient safety and drug safety became a popular focus for journalists, health care leaders and concerned citizens [12]. As described above, especially the elderly are a vulnerable group and patient safety and drug safety are of major importance in geriatric healthcare.

Hence, in the elderly, the risks of drug therapy should be carefully weighed against the benefits and appropriate measures should be taken to decrease the risk of adverse effects. In this thesis, several pharmaco-epidemiological studies were described to provide more insight into this subject.

In the previous chapters, each specific study was described in detail, including the shortcomings and merits. In this chapter, the main findings are discussed and placed in the broader context of clinical practice.

Main findings

The Beers criteria and adverse consequences of inappropriate benzodiazepine use

The Beers criteria are a set of comprehensive explicit criteria for determining potentially inappropriate drug use in ambulatory elderly aged 65 years and over. These criteria were developed by a panel of experts in geriatric medicine in the USA after consensus meetings and based on their expertise and existing scientific literature [13]. The first set of criteria was developed for nursing home residents and published in 1991 [14]. In 1997, the criteria were updated and extended to ambulatory elderly [13]. Recently, the criteria have been updated again to include new drugs and incorporate new information available from the scientific literature [15]. In the USA, several studies have been performed to evaluate the extent of inappropriate drug use among ambulatory elderly according to the Beers criteria [16-19]. Until recently, few European data were available [20] and for the Netherlands there were no data at all concerning potentially inappropriate prescribing in the elderly.

In chapter 2.1, we described the results from a population-based cohort study on the extent and trend of inappropriate drug prescribing in the Netherlands according to these Beers criteria. It appeared that around 20% of the ambulatory elderly receive at least one inappropriate drug prescription per year, which is a substantial proportion. However, the Beers criteria have been criticized, since they do not identify all causes of inappropriate prescribing (e.g. drug-drug interactions are not included). Moreover, they sometimes define prescribing as inappropriate in situations where such drugs are actually appropriate [21]. Moreover, the relevance of using these criteria in clinical practice is unproven because they have not yet been properly validated in patient outcome studies. Therefore, we performed a study described in chapter 2.2, in which we investigated the clinical value of the Beers criteria for benzodiazepine use, by studying the association between inappropriate benzodiazepine use and the risk of fracture. We found that the risk of fracture in 'inappropriate' benzodiazepine users according to the Beers criteria compared to 'appropriate' users, was not significantly different. However, using other criteria based on the more recent insights in the literature, i.e. dose and duration of use being more important than type of benzodiazepine [22-25], we found a more than 3-fold higher risk of fracture in persons with a high daily dose and longer duration of use than in those on a low daily dose and a short duration of use (14 days or less), regardless of the type of benzodiazepine prescribed. These results seem to indicate that in clinical practice, dosage and duration of use are more important criteria for appropriate benzodiazepine use than the Beers criteria, which only focus on elimination half-life and dosage of specific benzodiazepines

The study described in chapter 2.2 underlines the need for patient outcome

studies to test the usefulness of this type of explicit criteria in clinical practice. Using prescribing criteria should really improve patient outcomes in clinical practice and pharmaco-epidemiological studies can help to get more insight into this matter. Criteria for quality of prescribing in the elderly should be evidence-based and regularly updated according to new information in the scientific literature. Also alternative explicit criteria have been developed to improve the quality of drug prescribing in the elderly, by also taking into account other aspects of medication use in older patients, such as underuse of necessary medications and drug monitoring and documentation [26]. Also these aspects of medication care deserve attention [27] and more research in this field is needed.

ADR-related hospitalisations

Hospitalisations caused or complicated by adverse drug reactions (ADRs) represent a substantial burden in health care. Several studies and meta-analyses have estimated that hospitalisations attributed to adverse drug reactions (ADRs) account for between 2.4 % and 6.4 % of all hospital admissions in Western countries [8,28-31]. For the elderly, this percentage has been estimated at 3.4 % to 16.6 % [30,32]. Approximately 80% of ADRs causing admission or occurring in hospital are type A (dose-related) reactions. Consequently, these are predictable from the known pharmacology of the drug and may be preventable [8,33]. Most epidemiological studies evaluating the extent of ADR-related hospitalisations were conducted within (single) units, departments or hospitals, hence different settings and methods were used. Because of the variability of the results and methodology and a lack of representativeness, it is difficult to confidently generalise these results to a national level.

In chapter 3, we described 2 studies in which we tried to estimate the extent, characteristics and determinants of ADR-related hospitalisations in the Netherlands by using 2 different approaches. In chapter 3.1, we studied the proportion of ADR-related hospitalisations in the Netherlands using a nationwide computer database for all hospital discharge records, the LMR (Landelijke Medische Registratie) database. We found that almost 2% of all acute admissions in 2001 were coded as ADR-related. This proportion increased with age from less than 1% in the age group below 18 years to more than 3% in the age group of 80 years and older, confirming that older persons have more ADR-related problems. The most common ADR-related hospitalisations appeared to be gastro-intestinal bleedings during use of anticoagulants, more or less consistent with other studies [31,32,34]. Although substantial, the proportion of ADR-related hospitalisations was lower than the proportion found in studies that used chart review or prospective methods [31,32,35,36], probably because not all ADRs are recognized or mentioned in discharge diagnoses and coded accordingly [37]. Furthermore, we found that only approximately 1% of the

ADRs causing hospitalisation was reported to our national centre for spontaneous ADR reporting (Netherlands Pharmacovigilance Centre LAREB), although all Dutch health care providers are strongly encouraged to report serious ADRs, such as ADRs leading to hospitalisation, permanent disability or death [38]. However, the aim of a spontaneous reporting system is mainly to detect new signals (mostly type B reactions) and not to be overwhelmed by already well-known serious type A reactions regularly causing hospitalisations (e.g. gastrointestinal bleeding while using anticoagulants). Hence, we should place this underreporting into that perspective.

For the study described in chapter 3.2, we used hospital discharge letters and electronic general practitioner information from the IPCI database to evaluate the incidence, characteristics and determinants of ADR-related hospitalisations. By using this detailed population-based approach, we could also evaluate the value of our national coding system for hospital discharge records in estimating the extent of drug-related hospitalisations. By using electronic patient records and manually reviewing more than 3500 hospital discharge letters, we estimated that 5.1% of all acute hospital admissions in the Netherlands is caused by ADRs, fitting in the range of estimates in other large studies [8,30,31,36]. It appeared to be a higher estimate than we found in the study using the national coding system (1.8% ADR-related). This was expected because it is likely that not all ADRs are recognized or mentioned in discharge diagnoses and coded accordingly in the LMR. However, the estimates we found using the LMR data are much higher than studies in other countries that used similar coding sytems. Waller et al. concluded that there is a significant underestimation of the problem in the hospital [37,39].

We found that especially older patients are at increased risk of ADRs resulting in hospitalisations. In this group, 9.8% of all acute admissions was attributed to an ADR (as against 5.1% in the total study population). Moreover, the preventability of ADRs was judged highest in the elderly (40% of the ADRs). Consequently, we could conclude that older patients appear to be particularly at risk of serious ADRs and that a substantial part of these ADRs is potentially preventable. This patient group deserves extra attention and should be targeted for preventive actions in order to improve drug therapy in the elderly.

Drug-induced atrial fibrillation

Atrial fibrillation (AF) is an arrhythmia with a high prevalence and incidence in the elderly population. This arrhythmia, with a great burden and serious complications, is mainly associated with cardiovasculair disease and older age [40,41]. However, several drugs have been associated with the induction of AF in case reports, also in patients without apparent heart disease. It is important to recognize drugs as a

potential cause of atrial fibrillation, especially in the elderly, because increasing age is associated with multiple drug use and a high incidence of AF. Therefore, we reviewed which drugs have been associated with AF in the literature and what is known about the potential inducing mechanisms (chapter 4.1). Several described mechanisms are brought forward in this review, some still speculative. The most important ones are adrenergic or vagal stimulation by sympathicomimetics, parasympathicomimetics and their inhibitors, direct cardiotoxicity (cytostatics), changing atrial conduction, refractoriness or automaticity (anti-arrhythmics), coronary vasoconstriction/ischemia (acetylcholine, sumatriptan), and (local) electrolyte disturbances (diuretics, high-dose corticosteroids).

Pharmaco-epidemiological studies quantifying the role of drugs in the development of AF, have not been performed until very recently [42]. An important problem in studying a potential association, is confounding by indication. Most of the drugs mentioned above are given for a disease that is a risk factor for atrial fibrillation. For example, cardiovascular drugs are given for cardiac indications and many of these may cause atrial fibrillation themselves. It is very difficult to study to what extent these (cardiovascular) drugs increase the risk to develop AF. However, some drugs mentioned in the review have a wide array of indications, such as corticosteroids. Corticosteroids are powerful, important drugs in clinical practice. They are regularly prescribed to elderly, for chronic obstructive lung disease, but also for other indications. Many (long-term) adverse effects are already known, such as osteoporosis, drug-induced diabetes mellitus, hypertension and obesity [43]. However, high-dose corticosteroid use has occasionally also been associated with the development of AF in case reports [44-48]. It was postulated that high dose corticosteroids mediate potassium efflux via a direct effect on the cell membrane, which may induce arrhythmogenesis [49]. We performed a nested case-control study within the Rotterdam Study and found that current use of high dose corticosteroids is strongly associated with an increased risk of new-onset AF (chapter 4.2). We were able to study the association both in persons with asthma or COPD, and in those with other indications for corticosteroid therapy, at the same time adjusting for important potential confounders. This makes it highly unlikely that the indications asthma or COPD, which are independent risk factors for AF [41,50], confounded our results. By performing this study we were able to quantify the association between corticosteroid use and atrial fibrillation and to detect an important potential risk group for developing atrial fibrillation: elderly patients receiving high doses of corticosteroids.

Methodological considerations

Pharmaco-epidemiological studies have an important role in studying unintended (adverse) effects of drugs. The validity of observational, pharmaco-epidemiological studies is frequently questioned because of potential bias and confounding, but careful design and analysis may deal with most of these problems. In the next paragraphs, some of the main issues will be discussed concerning internal validity of the pharmaco-epidemiological studies in this thesis.

Study setting

Most studies described in this thesis used data from 2 population-based data sources: 1) the Rotterdam Study, a prospective population-based cohort study among 7983 older adults living in Ommoord, a suburb of Rotterdam [51] and 2) the Integrated Primary Care Information (IPCI) project, a general practice research database including all computer-based patient records from a group of 150 general practitioners in the Netherlands, covering more than 500.000 patients [52,53].

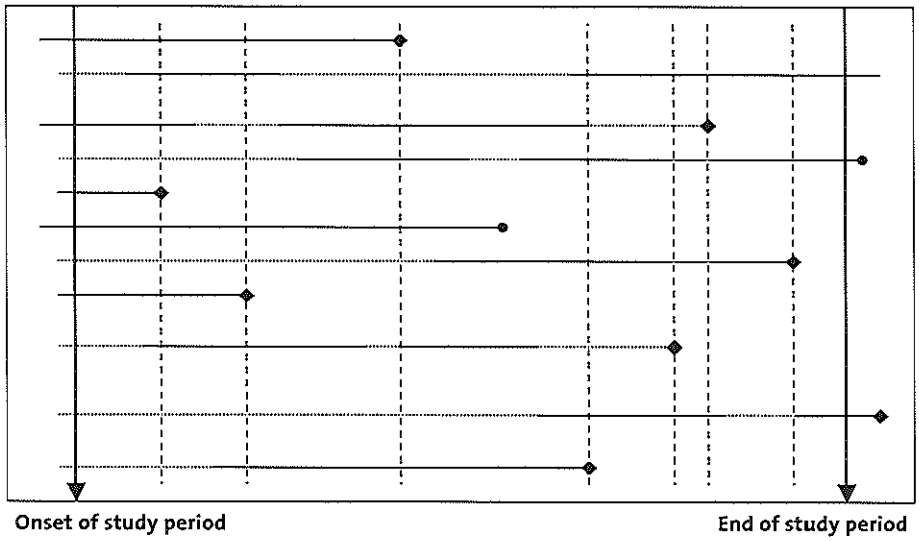
In the Rotterdam Study a large population of older adults is included in a follow-up. The advantages are that the follow-up duration is relatively long and that extensive information is available on all participants. In addition to follow-up surveys, the total cohort is continuously being monitored for major morbidity and mortality through linkage of general practitioner and municipal mortality records. Furthermore, all participants fill their prescriptions in automated pharmacies linked to one computer network. Data on all dispensed drugs since 1 January 1991 are available in computerized format on a day-to-day basis. All information is gathered before, and irrespective of, the outcome under study for the large majority of the study participants. This limits the chance of selection bias and information bias. We used data from the Rotterdam Study to investigate the association of inappropriate benzodiazepine use with the risk of fracture (chapter 2.2) and to study the association between corticosteroid use and the risk of atrial fibrillation (chapter 4.2).

The IPCI project is a large database which contains the computer-based full medical patient records from a group of 150 general practitioners (GPs) in the Netherlands. In the IPCI database, extensive information is available on the prescribed drugs and patient co-morbidity. The potential for selection bias is negligible as participation in the IPCI project is based on passive consent and because almost all health care in the Netherlands is provided by or via the general practitioner. Hence, non-participation is not an issue in the IPCI project. We used the IPCI database to assess the extent of potentially inappropriate drug prescribing in the elderly (chapter 2.1) and the prevalence and incidence of ADR-related hospitalisations (chapter 3.2) in the Netherlands.

Study design

For the analytical studies described in this thesis (chapter 2.2 and 4.2), we used a nested case-control design embedded in the fixed cohort of elderly participating in the Rotterdam Study. To each case, we matched all persons in the cohort who were at risk to become a case on the index date of the corresponding case. The controls received the index date of the case to which they were matched. Because we had very detailed information on drug use on a day-to-day basis, we were able to determine for all persons under study on the index dates of the cases, which drugs were used, in what dosage and what the duration of use was. In **figure 1**, this type of analysis is visualised. Using this design, selection bias was unlikely because cases and controls were derived from a prospective population-based cohort study, and controls came from the same study base as cases.

Figure 1 Study design of the analytical pharmaco-epidemiological studies (basic scheme)



◆ **Cases**

• **Deaths**

The *horizontal* solid lines represent the exposed time to the drug under study and the dotted lines the non-exposed time.

The *vertical* dotted lines show that every time on an index date of a case, the drug exposure of the case is compared to the drug exposure of all persons in the cohort that are alive and at risk to become a case.

Bias and confounding

In observational studies there is always the potential for selection bias, information bias and confounding. Considering the population-based characteristics of both the Rotterdam study and the IPCI project, selection bias is negligible.

Information bias, also known as misclassification bias, observation or recall bias, results from an incorrect determination of exposure or outcome [54]. This information bias might be random (non-differential) or systematic (differential). Non-differential misclassification generally biases the results towards the null hypothesis (i.e. the actual risk is underestimated), whereas differential misclassification may result in over- as well as in underestimation of the actual risk [55].

Concerning the drug exposure in our studies, we had very detailed and comprehensive data on drug exposure on a day-to-day basis, both in the Rotterdam Study as well as in the IPCI database. Drug exposure is prospectively and automatically gathered in both data sources, and thus independently of the outcomes of interest in our studies. Hence, misclassification of exposure would be only non-differential, and thus potentially underestimate our risk estimates. In the Rotterdam Study, drug dispensing data are available, whereas in the IPCI project the studies are performed with prescription data. In IPCI, specialist medication may be somewhat underestimated and it is not always certain whether prescriptions are actually filled.

Misclassification of the outcomes of interest in our studies would also be non-differential, because the outcomes were assessed independently of the exposure and patient co-morbidity. Some random misclassification might have occurred which tends to underestimate rather than overestimate the risk estimates.

Confounding by indication is a common problem in pharmaco-epidemiologic research and arises when the indication of the treatment is a risk factor for the outcome under study [56,57]. For example, confounding by indication was an issue in our study on corticosteroids and the risk of atrial fibrillation. High dose corticosteroids are mainly prescribed for (exacerbation of) chronic obstructive lung disease in the elderly, which is an independent risk factor for atrial fibrillation [41,50]. Hence, the indication potentially confounds the association between corticosteroid use and the risk of atrial fibrillation. However, corticosteroids are also prescribed for a wide array of other indications which are not known as risk factors for AF. Fortunately, we had power enough to also study the association in these patients and found an increased risk of AF in these patients as well. By doing so, we solved the potential problem of confounding by indication.

Future directions

Pharmacotherapy in the elderly is common practice and an important aspect of medical care, with many beneficial effects. In the future, its share in health care practice will further increase with the growing older population and the development of new drug therapies. However, adverse consequences of drug use should be taken very seriously. Adequate drug prescribing practice is of major importance, especially in elderly patients, and can prevent a major burden of adverse events and health care costs.

Including more elderly patients in clinical trials before the marketing of new drugs might be a good initiative to increase the knowledge about optimum drug dosages and drug-drug or drug-co-morbidity interactions in the elderly. However, research in daily clinical practice might be even more important, because the setting in the real world of medical practice is different from the setting in randomised clinical trials. Clinical trials are performed in a highly controlled clinical setting, which may not mimic the setting in which the drug will ultimately be used.

In the last few years, several initiatives have been taken to develop criteria for improving quality of pharmacotherapy in the elderly. Whether these criteria really improve patient outcomes in clinical practice, is sometimes questioned. Our research in this thesis showed that pharmaco-epidemiological studies can be very useful in providing extra information for the development of such criteria (chapter 2.2). Pharmaco-epidemiological studies can also quantify the problem of potentially serious adverse drug effects (chapter 3 and 4.2). Furthermore, pharmaco-epidemiological research can help policy makers in their initiatives to reduce the incidence of adverse events in medical practice.

As stated before, in the future the importance of safe drug therapy in the elderly will further increase with the growing older population. Pharmaco-epidemiological research will remain an important tool in the assessment of the risk-benefit profile of drug therapy in the older patient.

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6

Summary
Samenvatting

Summary

Pharmacotherapy in the elderly is an important aspect of medical care and has many beneficial effects. However, in view of multiple co-morbidity, changes in pharmacokinetics and pharmacodynamics and concomitant use of several drugs simultaneously (polypharmacy), elderly people are at increased risk of drug-related problems. In this thesis, we focus on the quality of drug prescribing and on adverse consequences of pharmacotherapy in the elderly. In the aging western countries, the elderly are a vulnerable patient group of increasing importance. Most studies described in this thesis used data from the Rotterdam Study, a prospective population-based cohort study and the Integrated Primary Care Information (IPCI) project, a general practice research database. Both data sources are situated at the Erasmus MC in Rotterdam.

Chapter 1 gives a general introduction to pharmacotherapy in the elderly. **Chapter 2** focuses on the Beers criteria, which are internationally known criteria for quality of drug prescribing in the elderly. **Chapter 2.1** describes the extent of potentially inappropriate drug prescribing in the Netherlands, based on the Beers criteria. We found that approximately 20% of the elderly in the Netherlands receive at least one inappropriate drug prescription per year according to these criteria. In **chapter 2.2,** the consequences of inappropriate prescribing according to the Beers criteria were assessed by studying the association between inappropriate use of benzodiazepines and the risk of fracture. We found that the risk of fracture in 'inappropriate' benzodiazepine users according to the Beers criteria compared to 'appropriate' users, was not significantly different. However, using other criteria based on the more recent insights in the literature, i.e. dose and duration of use being more important than type of benzodiazepine, we found a more than 3-fold higher risk of fracture in persons with a high daily dose and longer duration of use than in those on a low daily dose and a short duration of use (14 days or less), regardless of the type of benzodiazepine prescribed. These results seem to indicate that in clinical practice, dosage and duration of use are more important criteria for appropriate benzodiazepine use than the Beers criteria, which only focus on elimination half-life and dosage of specific benzodiazepines.

Chapter 3 focuses on hospitalisations caused or complicated by adverse drug reactions (ADRs). **In chapter 3.1** we studied the proportion of ADR-related hospitalisations in the Netherlands using a nationwide computer database for all hospital discharge records, the LMR (Landelijke Medische Registratie) database. We found that almost 2% of all acute admissions in 2001 were coded as ADR-related. This proportion increased with age from less than 1% in the age group below 18 years to more than 3% in the age group of 80 years and older, confirming

that older persons have more ADR-related problems. The most common ADR-related hospitalisations appeared to be gastro-intestinal bleedings during use of anticoagulants, more or less consistent with other studies. Although substantial, the proportion of ADR-related hospitalisations was lower than the proportion found in other studies using chart review or prospective methods, most likely because not all ADRs are recognized or mentioned in discharge diagnoses and coded accordingly. **Chapter 3.2** describes a study in which we used hospital discharge letters and electronic general practitioner information from the IPCI database to evaluate the incidence, characteristics and determinants of ADR-related hospitalisations. By using this detailed population-based approach, we could also evaluate the value of our national coding system for hospital discharge records in estimating the extent of drug-related hospitalisations. By using electronic patient records and manually reviewing more than 3500 hospital discharge letters, we estimated that 5.1% of all acute hospital admissions in the Netherlands is caused by ADRs, fitting in the range of estimates in other large studies. As expected, it appeared to be a higher estimate than we found in the study using the national coding system in chapter 3.1.

Chapter 4 focuses on atrial fibrillation, an arrhythmia with a high occurrence in the elderly population. This arrhythmia can be induced by drugs. **Chapter 4.1** reviews which drugs have been associated with atrial fibrillation in the literature, since little is known about drug-induced atrial fibrillation. Several described mechanisms are brought forward, some still speculative. The most important ones are adrenergic or vagal stimulation by sympathicomimetics, parasympathicomimetics and their inhibitors, direct cardiotoxicity (cytostatics), changing atrial conduction, refractoriness or automaticity (anti-arrhythmics), coronary vasoconstriction/ischemia (acetylcholine, sumatriptan), and (local) electrolyte disturbances (diuretics, high-dose corticosteroids). Subsequently, we investigated the association between corticosteroid use and the risk of atrial fibrillation in **chapter 4.2**, because there is hardly anything known about this association. We found that current use of high dose corticosteroids in an elderly population is strongly associated with an increased risk of new-onset atrial fibrillation (more than 6-fold risk increase). We were able to study the association both in persons with asthma or COPD, and in those with other indications for corticosteroid therapy, at the same time adjusting for important potential confounders. By identifying this high-risk group for developing atrial fibrillation, preventive measures can be taken to reduce the burden of atrial fibrillation in this group.

In **chapter 5**, we reflect on our main findings and discuss several methodological issues related to the topic of this thesis, and speculate on the implications of our results.

Samenvatting

Farmacotherapie bij ouderen is een belangrijk aspect van de medische zorg. Echter, door toenemende co-morbiditeit, veranderingen in farmacokinetiek en dynamiek en het gebruik van meerdere geneesmiddelen tegelijk (polyfarmacie), zijn ouderen extra kwetsbaar voor ongewenste effecten van geneesmiddelen. Dit proefschrift richt zich op de kwaliteit van voorschrijven en de ongewenste effecten van geneesmiddelengebruik bij ouderen. In de vergrijzende Westerse wereld zijn ouderen een kwetsbare patiëntengroep die steeds belangrijker wordt. De meeste studies, die in dit proefschrift beschreven zijn, werden uitgevoerd met behulp van data uit het Erasmus Rotterdam Gezondheid en Ouderen (ERGO) onderzoek en van het 'Integrated Primary Care Information' (IPCI) project, een elektronisch huisartsenbestand. Beide onderzoeksprojecten zijn onderdeel van het Erasmus MC.

Hoofdstuk 1 geeft een algemene inleiding over farmacotherapie bij ouderen. **Hoofdstuk 2** richt zich op de 'Beers' criteria, internationaal bekende criteria voor verantwoorde farmacotherapie aan ouderen. **Hoofdstuk 2.1** geeft een schatting van de mate van gecontraïndiceerd voorschrijven aan ouderen in Nederland volgens de Beers criteria. Wij vonden dat ongeveer 20% van de ouderen in Nederland tenminste één gecontraïndiceerde prescriptie per jaar ontvangt. In **hoofdstuk 2.2** worden de mogelijke ongewenste effecten van onverantwoord voorschrijven volgens de Beers criteria onderzocht door de associatie tussen 'onjuist' benzodiazepine gebruik en botfracturen (door vallen) te onderzoeken. Wij vonden dat het risico op fractuur niet significant verschillend was tussen ouderen die 'onverantwoorde' benzodiazepines kregen voorgeschreven en ouderen die benzodiazepines volgens de Beers criteria op een verantwoorde manier kregen voorgeschreven. Echter, recent onderzoek uit de literatuur wijst erop dat dosis en gebruiksduur belangrijker zijn voor het risico op fractuur dan het type benzodiazepine. Bij ouderen, die behandeld werden met een hoge dagelijkse dosis en een langere gebruiksduur was sprake van een 3 maal hoger risico op fracturen dan bij ouderen met een lage dagdosis en kortdurend gebruik (minder dan 14 dagen), ongeacht het type benzodiazepine dat voorgeschreven werd. Deze resultaten suggereren dat dosis en gebruiksduur in de klinische praktijk belangrijkere criteria zijn voor verantwoord gebruik van benzodiazepines dan het gebruik van de Beers criteria, die zich alleen richten op halfwaardetijd en dosis van specifieke benzodiazepines.

Hoofstuk 3 richt zich op ziekenhuisopnames die veroorzaakt of gecompliceerd zijn door bijwerkingen van geneesmiddelen. In **hoofdstuk 3.1** bestudeerden wij het percentage van aan bijwerkingen gerelateerde ziekenhuisopnames in Nederland door gebruik te maken van een nationaal computerbestand met

ontslagdiagnoses en coderingen van alle ziekenhuisopnames, de Landelijke Medische Registratie (LMR). Wij vonden dat bijna 2% van alle acute opnames in 2001 waren gecodeerd als vermoedelijke bijwerking. De meest voorkomende - als bijwerking gecodeerde opnames - bleken gastrointestinale bloedingen te zijn tijdens gebruik van antistolling, min of meer in lijn met andere studies. Hoewel het om een substantieel percentage aan bijwerkingen toegeschreven opnames gaat, is het percentage lager dan het percentage waarbij statusondezoek of prospectieve methoden zijn gebruikt, waarschijnlijk omdat niet alle bijwerkingen herkend of genoemd worden in de ontslagdiagnoses en als zodanig gecodeerd zijn in de LMR. **Hoofdstuk 3.2** beschrijft een studie waarbij wij middels de IPCI database de incidentie, karakteristieken en determinanten van aan bijwerkingen toegeschreven ziekenhuisopnames hebben onderzocht. Door deze gedetailleerde populatiegerichte benadering konden wij ook de waarde evalueren van het LMR coderingssysteem in het schatten van het percentage van alle aan bijwerkingen gerelateerde opnames. Met behulp van elektronische patiëntgegevens en na bestudering van meer dan 3500 ontslagbrieven, schatten wij dat 5.1% van alle acute opnames in Nederland wordt veroorzaakt door bijwerkingen. Dit is vergelijkbaar met de schattingen van internationale studies. Zoals verwacht, is dit percentage hoger dan het percentage in hoofdstuk 3.1.

Hoofdstuk 4 richt zich op atriumfibrilleren, een hartritmestoornis die relatief veel voorkomt bij ouderen. Deze ritmestoornis kan veroorzaakt worden door geneesmiddelen. **Hoofdstuk 4.1** geeft een overzicht van de geneesmiddelen die in de literatuur met atriumfibrilleren in verband zijn gebracht. Er is weinig bekend over geneesmiddel-geïnduceerd atriumfibrilleren. Enkele potentiële mechanismen worden besproken. De belangrijkste zijn adrenerge of vagale stimulatie door sympaticomimetica, parasympaticomimetica en hun inhibitoren, directe cardiotoxiciteit (cytostatica), verandering van conductie, refractietijd of ritme (anti-arrhythmica), coronaire vasoconstrictie / ischemie (acetylcholine, sumatriptan), en (locale) elektrolytstoornissen (diuretica, hoge dosis corticosteroiden). Vervolgens onderzochten wij de associatie tussen corticosteroid gebruik en het risico op het ontwikkelen van atriumfibrilleren in **hoofdstuk 4.2**, omdat er weinig bekend is over deze associatie. Wij vonden dat ten tijde van het gebruik van hoge doses corticosteroiden door ouderen het risico op atriumfibrilleren sterk verhoogd is (meer dan 6 keer zo hoog). Wij waren in staat deze associatie zowel in asthma/COPD patiënten te onderzoeken als in patiënten met andere indicaties voor corticosteroid therapie, terwijl er ook werd gecorrigeerd voor belangrijke verstorende variabelen. Door het detecteren van deze risicogroep zouden preventieve maatregelen genomen kunnen worden om het risico op of complicaties van atriumfibrilleren te verminderen.

In **hoofdstuk 5** worden onze belangrijkste bevindingen samengevat en bespreken we een aantal methodologische aspecten. Ook wordt besproken wat de implicaties zijn van onze bevindingen en welke plaats de farmaco-epidemiologie heeft in toekomstig onderzoek.

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Cornelis van der Hooft was born on May 14, 1974 in Potgietersrus, South-Africa. He graduated in 1992 at the "Marnix Gymnasium" in Rotterdam. In 1993, he started his medical education at the Erasmus University Rotterdam, where he obtained his medical degree in 2000. During his education, he went to Cape Town, South-Africa, where he performed a study on diagnostics for variegate porphyria, a relatively common genetic disease in South-Africa, and later for an internship at the "Groote Schuur Hospital". After obtaining his medical degree, he worked for a year as a resident in Internal Medicine at the "Havenziekenhuis" in Rotterdam. In October 2001, he started the work described in this thesis at the department of Epidemiology & Biostatistics of the Erasmus MC, Rotterdam. During this period he also worked at the Pharmacovigilance department of the Dutch Health Care Inspectorate in The Hague. In 2004, he obtained a Master of Science degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences. In April 2006, he will start his specialist training in Clinical Geriatrics at the "Medisch Centrum Leeuwarden" in Leeuwarden.