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Drug-related morbidity and mortality: Pharmacoepidemiological aspects

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Searching for rare events (whales) in the mist.

The Saint Lawrence River, Quebec, Canada, 2007.

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*As we know,
There are known knowns.
There are things we know we know.
We also know
There are known unknowns.
That is to say
We know there are some things
We do not know.
But there are also unknown unknowns,
The ones we don't know
We don't know.*

Donald Rumsfeld, 2002
The Accidental Epidemiologist
Secretary of Defence, 1975-1977, 2001-2006

Abstract

Adverse drug reactions (ADRs) constitute a significant health problem with consequences for the patient as well as for society. Suspected ADRs have been reported to occur in about 2-14% of hospitalised patients. In about 5% of deceased hospitalised patients suspected ADRs may have caused or contributed to the fatal outcome. When a pharmaceutical drug is approved for marketing, the drug has been tested only on a limited number of patients (often <6000) for a limited time period in a controlled environment. Hence mostly common ADRs are detected in these trials. Moreover, certain patient groups, for example patients with co-morbidities, elderly patients, children and pregnant women are often not included in these studies. Thus, it is important to closely monitor the use of drugs after marketing to observe new effects and detect new ADRs.

The aim of this thesis is to describe the pattern of pharmaceutical substance use related to morbidity and mortality and to investigate two serious ADRs. We have studied the incidence of fatal ADRs, fatal intoxications, cerebral haemorrhage related to warfarin treatment and venous thromboembolism (VTE) related to treatment with antipsychotic drugs.

Observational studies form the basis for this thesis. Data from the Swedish Cause of Death Register, medical case records, the Swedish database on ADRs, the forensic pathology and forensic toxicology databases, and Swedish and Danish hospital discharge registers, Danish prescription registers, and civil registry systems were used.

In Paper I we found that 3% of all fatalities in a Swedish population were related to a suspected ADR. Of the deceased hospitalised patients, 6% were related to a suspected ADR. Haemorrhage was the most commonly observed fatal suspected ADR, accounting for almost two-thirds of the events and anticoagulantia was the most common drug group associated with fatal suspected ADRs (almost 50%). A suspected intoxication could have contributed to the fatal outcome in 0.6% of the deceased. Among the fatal intoxications in Swedish medico-legal autopsies studied in Paper II, on average four substances were detected per case. The five most commonly detected substances in individuals with a fatal intoxication were ethanol, propoxyphene, paracetamol, diazepam and flunitrazepam. Among patients diagnosed with cerebral haemorrhage, 10% (59 cases) were treated with warfarin at onset of symptoms (Paper III). Of these, 7 cases (12%) were considered to have been possibly avoidable since the patients were treated with concomitant drugs that have the potential to enhance warfarin effects. The results from Paper IV and Paper V in combination with the published literature suggest that patients treated with antipsychotic drugs have an increased risk for VTE. Compared with non-users, an adjusted odds ratio for VTE of 2.0 was found for users of any antipsychotic drugs in a Danish population. In a medico-legal autopsy series, an adjusted odds ratio for fatal pulmonary embolism of 2.4 and 6.9 was found for users of first-generation low-potency antipsychotics and second-generation antipsychotics, respectively.

In summary, drug-related morbidity and mortality is a significant problem and suspected ADRs contribute to a substantial number of deaths. Fatal intoxications are relatively common and it is important to observe changes in patterns of substances associated with fatal

intoxications to be able to discover new trends and monitor effects of preventive work. A significant proportion of warfarin-related cerebral haemorrhage was caused by drug-drug interactions and was considered possible to avoid. Users of antipsychotic drugs may increase the risk of VTE.

Populärvetenskaplig sammanfattning

Idag finns det säkra och effektiva behandlingar mot många sjukdomar. Läkemedel är den vanligaste behandlingsformen i sjukvården och under 2006 hämtade sex miljoner svenskar (68%) ut ett eller fler recept på ett apotek i Sverige. Även om läkemedelsbehandling har många positiva effekter kan även oönskade och skadliga effekter vid läkemedelsbehandling uppkomma, dvs. läkemedelsbiverkningar. Innan ett läkemedel kommer ut för försäljning har man studerat effekter och biverkningar på ett begränsat antal individer (ofta <6000) under en begränsad tidsperiod där patienterna övervakas noga. Dessutom är det i regel enbart patienter med få andra sjukdomar och läkemedel som ingår i dessa studier. Därför är oftast enbart de vanligaste biverkningarna kända när ett läkemedel börjar säljas till allmänheten. När ett läkemedel blir tillgängligt för ett stort antal patienter är det därför viktigt att man med olika metoder fortsätter att följa läkemedlets effekter och biverkningar. Tidigare har man visat att ungefär 2-14% av inläggningar på sjukhus beror på läkemedelsbiverkningar. Dessutom kan biverkningar ha bidragit eller orsakat dödsfallet i ungefär 5% av de som avlider på sjukhus. Biverkningar orsakar mycket lidande för patienten och kostar samhället både tid och pengar. Om det skulle vara möjligt att förhindra några av dessa sjukhusinläggningar eller dödsfall skulle man vinna mycket. Det är svårt att uppskatta hur många biverkningar som kan förhindras. Genom att studera faktorer som kan öka risken för en oönskad effekt kan man bättre anpassa behandlingen till den enskilde patienten och därmed förhindra biverkningar.

Syftet med den här avhandlingen är att beskriva mönster av läkemedelsrelaterade sjukdomar och dödsfall, och att undersöka risken för två allvarliga läkemedelsbiverkningar. Förekomsten av misstänkta läkemedelsbiverkningar, vilka faktorer som kan öka risken för att få en läkemedelsbiverkan, samt vilka läkemedel och biverkningar som förekommer har studerats. Detta gjordes utifrån uppgifter hämtade från dödsorsaksregistret, svenska biverkningsregistret, journaler, rättsmedicinska register, slutenvårdsregister och receptregister. Genom att utnyttja sådan information har vi i närmare detalj studerat förekomsten av dödsfall där ett eller flera läkemedel kan ha haft betydelse för dödsfallet, förgiftningsdödsfall, blödningar i samband med blodförtunnande medicinering och blodproppar i samband med antipsykotisk medicinering.

I de arbeten som ingår i avhandlingen har vi funnit att en läkemedelsbiverkan misstänks ha bidragit eller orsakat dödsfallet i ungefär 3% av de som avlidit i en svensk population (Arbete I). Blödningar står för nästan två tredjedelar av dessa biverkningar och blodförtunnande medel misstänks vara inblandade i nästan hälften av de misstänkta läkemedelsbiverkningarna. I den här svenska populationen avled 0,6% till följd av misstänkt läkemedelsförgiftning. Bland rättsmedicinskt undersökta förgiftningsdödsfall påvisades i genomsnitt fyra substanser per fall (Arbete II). De fem vanligaste påvisade substanserna i studien var alkohol, dextropropoxifen, paracetamol, diazepam och flunitrazepam. Bland patienter som får hjärnblödning behandlades 10% vid blödningstillfället med ett blodförtunnande medel, warfarin (Arbete III). I 7 fall (12%) skulle hjärnblödningen möjligen kunna ha förhindrats då patienterna samtidigt behandlades med andra läkemedel som kan ha ökat blödningsrisken. Den sammantagna

bilden av den litteratur som finns publicerad och resultatet av Arbete IV och Arbete V, tyder på att patienter som behandlas med antipsykotiska preparat har en ökad risk för att få blodpropp. Flera faktorer har föreslagits som kan förklara den ökade risken för blodpropp bland patienter som behandlas med antipsykotika som har med sjukdomen att göra och/eller behandlingen med antipsykotiska läkemedel.

Sammanfattningsvis visar detta avhandlingsprojekt att läkemedelsbiverkningar är ett väsentligt sjukvårdsproblem som bidrar till ett betydande antal dödsfall. Förgiftningsdödsfall med läkemedel är också relativt vanliga och det är viktigt att bevaka effekter av preventiva åtgärder och se om de substanser som används ändras över tid. En del läkemedelsrelaterade biverkningar skulle kunna förhindras då t.ex. en betydande andel av warfarinrelaterade hjärnblödningar beror på läkemedelsinteraktioner. Förekomsten av venösa blodproppar verkar vara förhöjd bland patienter som behandlas med antipsykotiska läkemedel, men fler studier behövs för att avgöra detta och vad det i så fall beror på.

List of papers

This thesis is based on the following papers that will be referred to according to their Roman numerals:

- I** Karin Wester, **Anna K. Jönsson**, Olav Spigset, Henrik Druid, Staffan Hägg. Incidence of fatal adverse drug reactions: a population based study. *British Journal of Clinical Pharmacology*. In press.
- II** **Anna Jönsson**, Per Holmgren, Johan Ahlner. Fatal intoxications in a Swedish forensic autopsy material during 1992-2002. *Forensic Science International*. 2004;143(1):53-9.
- III** **Anna K. Jönsson**, Olav Spigset, Ingela Jacobsson, Staffan Hägg. Cerebral haemorrhage induced by warfarin-the influence of drug-drug interactions. *Pharmacoepidemiology and Drug Safety*. 2007;16(3):309-315.
- IV** **Anna K. Jönsson**, Staffan Hägg, Erzebet Puho, Lars Pedersen, Henrik T. Sørensen. Antipsychotics and the risk for venous thromboembolism. A population based nested case-control study. Manuscript.
- V** **Anna K. Jönsson**, Lars Brudin, Johan Ahlner, Karin Hedenmalm, Anders Eriksson, Staffan Hägg. Antipsychotics associated with pulmonary embolism in a Swedish medico-legal autopsy series. Submitted to *International Clinical Psychopharmacology*.

Abbreviations

The most important abbreviations used in this thesis are listed below.

ADR:	Adverse drug reaction
ATC:	Anatomical therapeutic chemical classification system
AF:	Atrial fibrillation
ARR:	Adjusted relative risk
BMI:	Body mass index
CI:	Confidence interval
COPD:	Chronic obstructive pulmonary disease
CNS:	Central nervous system
CYP:	Cytochrome P450 system
DDD:	Defined daily doses
DVT:	Deep vein thrombosis
FADR:	Fatal adverse drug reaction
GC-MS:	Gas chromatography-mass spectrometry
GI:	Gastrointestinal
GP:	General practitioner
GPRD:	General Practice Research Database
HPLC:	High performance liquid chromatography
HRT:	Hormone replacement therapy
ICD-8 (-9, -10):	International classification of diseases, 8 th revision (9 th revision, 10 th revision)
ICH:	Intracerebral haemorrhage
INR:	International normalised ratio
LC-MS-MS:	Liquid chromatography-triple quadruple mass spectrometry
MPA:	Medical Products Agency
NSAIDs:	Non steroid anti-inflammatory drugs
OD:	On demand
OTC:	Over the counter
PE:	Pulmonary embolism
RCT:	Randomised controlled trial
SSRIs:	Selective serotonin reuptake inhibitors
SWEDIS:	Swedish drug information system
VTE:	Venous thromboembolism
WHO:	World Health Organisation

Terminology

Adverse drug reaction	-a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function [1].
Bias	-any trend in the collection, analysis, interpretation, publication or review of the data which are systematically different from the truth.
Causality assessment	-the evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction. Causality assessment is usually made according to established algorithms.
Confounding	-study participants with different characteristics are unevenly distributed between study groups affecting the observed association.
Drug-drug interaction	-the action of a drug that may affect the activity, metabolism, or toxicity of another drug.
Forensic medicine	-the medical speciality that uses medical and natural science knowledge for the purposes of law.
Pharmacovigilance	-the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem [2].
Pharmacoepidemiology	-the application of epidemiological methods on pharmacological issues.
Relative risk	-the risk of the outcome under study in an exposed population related to the risk of that outcome in an unexposed population.
Signal	-new information to a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously [3].

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Introduction

Drugs are safe and effective therapies in the treatment of many diseases. The most common therapy in health care is the use of pharmaceutical drugs. According to the National Corporation of Pharmacies, Stockholm, Sweden (Apoteket AB) 36 933 million SEK (3 937 million Euros) were spent on pharmaceutical drugs in Sweden during 2006. The use of pharmaceutical drugs is usually described as the number of DDDs sold (defined daily doses; the assumed average 24-hour dose taken by an adult for the main indication of the drug). The number of DDDs sold has almost doubled during a 20-year period from 1111 DDD/1000 inhabitants and day in 1985 to 1926 DDD/1000 inhabitants and day in 2005. Moreover, during 2006 6.1 million (68%) of the Swedish population purchased at least one prescribed drug [4]. Ideally, drugs should be prescribed and used in exact accordance with the best understanding of their appropriateness for the particular patient taking their benefit, harm, effectiveness and risk into account. However, mistakes in prescribing and handling of drugs may occur and patient safety may be at risk [5-7]. Moreover, even though drugs are prescribed and used correctly, patients might still experience an adverse drug reaction (ADR).

Adverse drug reactions

According to the World Health Organisation (WHO) [1] an ADR is defined as a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. This definition does not include errors in drug use or intoxications. To include medical errors and intoxications, the term adverse drug *event* is used [7]. However, the term “adverse events” is also used in the context of randomised clinical trials (RCTs) here defined as any untoward effects observed in patients using the drug, but not necessarily with a causal relation to the drug exposure [8].

ADRs are common, with an incidence reported to range between 2.4% and 13.8% [9-13] of all patients admitted to hospitals. A drug-related hospital admission has been calculated to cost 543 Euros more than an average medical admission in Germany in 2002 [12] resulting in a yearly cost of 400 million Euros. In Sweden a single drug-related hospital admission has been calculated to cost 220 Euros in 2002 [9].

ADRs are commonly divided in Type A and Type B reactions [8, 14]. Type A reactions are reactions due to an exaggerated pharmacological effect of the drug. These reactions are common, accounting for 76-95% [9-12, 14] of ADRs, usually dose-related and less serious. Since these reactions can be understood through the pharmacological properties of the drug they are predictable and thus avoidable, at least in theory [15]. In general, the proportion of ADRs considered avoidable is high, but varies 18-73% [16, 17]. Factors affecting the risk for ADRs are dose, pharmaceutical variation in drug formulation, pharmacokinetic or pharmacodynamic abnormalities, and drug-drug interactions [14]. The elderly and patients with certain diseases such as renal failure are more likely to experience a type A reaction [14]. Type B reactions are bizarre and unexpected since they are not related to known pharmacological effect of the drug [8]. These reactions are uncommon, not related to dose, unpredictable, potentially more serious and are often due to hypersensitivity reactions or immunological reactions [18]. In recent years, ADRs have been further categorised as: C (accumulated dose-related reactions), D (delayed reactions), E (withdrawal reactions) and F (unexpected failure of therapy) [8].

Among patients admitted to hospital due to an ADR, the most commonly observed ADRs are gastrointestinal (GI) lesions, GI bleedings and cardiovascular disorders [9, 11-13]. The drugs most often implicated in suspected ADRs are NSAIDs (non steroid anti-inflammatory drugs), diuretics, cardiovascular agents and antithrombotic agents [9, 11-13]. Other common ADRs, which seldom lead to hospitalisation, are skin reactions [19, 20].

Fatal adverse drug reactions

Most ADRs are relatively mild and have minor impact on the health care and life quality of the patient. However, fatal ADRs (FADRs) do occur but are rare, 0.05-0.95% [10-12, 21-24] of patients admitted to hospital experience a FADR. Moreover, in a large US meta-analysis and in a single Finnish hospital study FADRs were suspected in 4.6% and 5.0% [10, 23] of deceased hospitalised patients. Most FADRs occur in elderly patients and seriously ill patients [15, 25]. Groups of drugs commonly reported to be implicated in FADRs are antineoplastic agents, anticoagulants, NSAIDs and drugs for treating obstructive airway diseases [11, 22, 23, 25, 26]. The diagnoses commonly associated with FADRs are GI haemorrhage, intracranial haemorrhage, dysrhythmia, myocardial infarction, renal failure and infections [11, 22, 23, 25, 26].

Intoxications

An intoxication may be defined as an intake (by ingestion, injection or inhalation) of an amount of substance(s) with the significant potential to cause harm to an individual. An intoxication may be accidental or intentional, fatal or non-fatal. Death may occur as a result of direct, indirect or even long-term effects of exposure to a particular substance or group of substances [27]. The terms intoxication and poisoning will be used interchangeably throughout this thesis.

Intoxications have been reported to comprise between 0.4% and 2.4% of patients admitted to a hospital [25, 28-32], most of these are mild, but 0.0-2.8% result in a fatal outcome [25, 28-

32]. Among deceased subjected to a forensic autopsy, 3-12% are fatal intoxications [27, 33]. Non-fatal intoxications in Denmark [34] and the approximate number of fatal intoxications in Sweden [35], have been relatively stable over time, whereas deaths caused by intoxications have been an increasing problem in the US [36, 37].

The substances causing intoxications vary between geographical areas. In agricultural regions individuals may have been exposed to pesticides [27, 32] whereas in other areas, particularly in larger cities, illicit drugs, carbon monoxide or pharmaceutical drugs are more common [27, 28, 32, 33, 37]. The pharmaceutical drug groups most commonly used in intoxications are analgesics, antidepressants and sedatives [25, 28, 29, 37, 38]. The amount of a drug needed to cause harm, and the extent of the harm done, differs between drug groups and between individuals. For example benzodiazepines cause depression of the central nervous system (CNS) following an overdose with symptoms like somnolence, diplopia, dysarthria, ataxia and impairment of intellectual functions [39]. Still only few deaths have been attributed to benzodiazepines alone [39-41] but when benzodiazepines are taken together with other CNS depressants, like ethanol, the additive effects may be fatal [39, 42]. Other drugs, for example propoxyphene, an opioid analgesic used to treat moderate to severe pain, has caused several deaths due to a combination of respiratory depression and its potent membrane stabilising activity, which leads to heart conduction defects and cardiac arrhythmia [43].

Drug-drug interactions

It is common that more than one drug is used simultaneously (*i.e.* concomitant medications) especially in hospitalised patients and in elderly patients [20, 44]. Moreover, in fatal and non-fatal intoxications a multitude of drugs and other substances are usually taken [25, 27, 28, 30]. When more than one drug is used simultaneously there is a possibility that the activity or metabolism of the drugs may be altered. The net result may be enhanced or reduced effects of one or both of the drugs or the appearance of a new effect that is not seen when either drug is taken alone.

More than 1000 drug interactions have been described, but only a small proportion of these have clinical importance [45]. Drug-drug interactions have been estimated to account for 5-30% of all ADRs [17, 45]. In a review, Becker *et al.* [46] reported that drug-drug interactions cause 0.05% of emergency department visits, and 0.57% of hospital admissions. In the elderly population drug-drug interactions are responsible for 4.8% of admissions to hospitals. The drugs most often involved are NSAIDs and cardiovascular drugs and the ADRs commonly observed are GI-bleedings, hypertension, hypotension and cardiac rhythm disturbances.

The mechanism of an interaction is either pharmacokinetic or pharmacodynamic. Pharmacokinetic drug-drug interactions may occur in any of the pharmacokinetic processes whereby the drug reaches its site of action and is then eliminated (absorption, distribution, metabolism and excretion). Absorption, metabolism and excretion are the best studied pharmacokinetic mechanisms. These reactions may result in an increase or decrease in drug concentrations leading to toxicity or insufficient efficacy to control the underlying disease.

Pharmacodynamic interactions occur when one drug alters the response of another by interaction at the receptor site or acts at a different site to enhance or diminish the effects of the first drug. Drugs binding at the same receptor site may be antagonists (inhibiting a response) or agonists (initiating a response) [45]. This leads to changes in efficacy without changes in drug concentrations.

Pharmacovigilance

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of ADRs or any other medicine related problem [2]. Before marketing, pre-clinical animal testing, *e.g.* investigating the mechanism of toxicity, followed by three phases of clinical testing in humans are performed. In clinical testing (phases I-III), first a small number of healthy volunteers and then patients are exposed to the drug under study to determine metabolism, information on pharmacokinetics, safe dosage ranges, efficacy and early information on safety. In phase III, RCTs are used where patients randomly are assigned to a treatment group (placebo/standard therapy or treatment under investigation). Patients with co-morbid conditions using several drugs, children or elderly patients are seldom included in RCTs [47]. RCTs are limited to a relatively small numbers of patients (often <6000) and the efficacy of the drug is only studied over a short time-period [47, 48]. Hence, only common ADRs (>1/1000 treated patient) may be detected and long term effects cannot be determined [48].

After approval (post-marketing), non-experimental pharmacoepidemiological studies (the application of epidemiological methods on pharmacological issues [49]) can be performed to evaluate the effects of drugs as part of ongoing medical care (Table 1). In medical care, drugs are used in a broader range of patients and circumstances than were studied in the clinical RCTs. With this broader patient base and larger number of patients treated in a “real life” setting it is possible to detect less common ADRs, measure incidence of known ADRs and beneficial effects more precisely since more patients are exposed to the drug [48].

Table 1. *Pharmacoepidemiological study-designs.*

Study design	Advantages	Disadvantages
Randomised controlled trials	Random assignment to treatment groups	Costly in time and money
Cohort study	Can study several outcomes and rare exposures Selection bias is less likely Unbiased exposure data Incidence data available	Possibly biased outcome data Expensive since it takes years to complete if done prospectively
Case-control study	Can study multiple causes and rare outcomes Less expensive	Selection of controls are problematic Possibly biased exposure data
Naturalistic study	Can provide rapid answers	No control of confounding No data on individual level
Case series	Easy quantitation of incidence	No control group
Case report	Cheap	No control group

In case reports (one patient) and case series (a collection of patients), diseases and/or exposure without a control group related to time, place or a person are described. Hypotheses can be generated on a previously unknown or incompletely documented possible causal relationship between an ADR and a drug. Moreover, in case series, the incidence of a certain ADR might be quantified. In 1961 [50] a physician published a letter to the editor of the Lancet of an unexpected increase in congenital abnormalities. These abnormalities were present in babies delivered by women who were given the drug thalidomide during pregnancy. This letter was the start of organised post-marketing surveillance of drug safety and spontaneous reporting systems were introduced in several countries, including Sweden [51]. In this thesis Paper I, Paper II and Paper III were designed as case series where subjects with suspected FADRs, fatal intoxications and warfarin-related cerebral haemorrhages were described.

In naturalistic studies aggregated group data test whether trends in an exposure (a presumed cause) and trends in disease (a presumed effect) coincide. These studies can provide rapid evidence for or against a hypothesis. To test a hypothesis, it may be necessary to perform studies that include a control group using observational (non-experimental) studies, where the treatment of the patient is not interfered with (cohort studies and case-control studies) or experimental studies where the treatment is controlled (RCTs). In cohort studies, cases (with an exposure) and controls (without an exposure) are identified and followed forward in time. Differences in outcomes between cases and controls are then observed. There are limitations: a large cohort is needed to identify rare outcomes, long study periods are needed to study delayed effects and if multiple outcomes are studied, several cohorts are needed [52]. In case-control studies, cases (with the disease) and controls (without the disease) are identified. The difference in the antecedent exposures is then compared and the risk for the outcome in the exposure groups is calculated (Figure 1). Case-control studies are useful when one wants to study a rare outcome or when multiple possible causes of a single disease are studied. In a nested case-control study cases and controls are drawn from the population of a cohort. In this thesis a case-control methodology was used to study a possible association between venous thromboembolism (VTE) in users of antipsychotic drugs in Paper IV and Paper V.

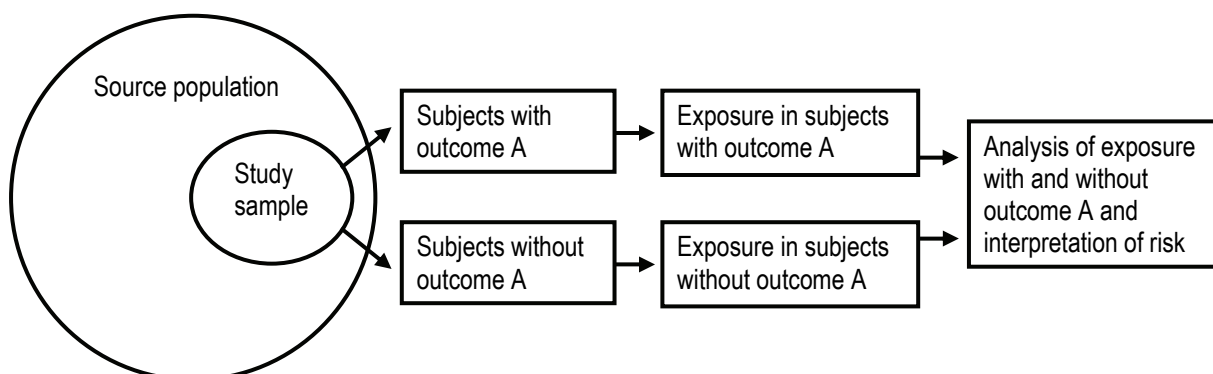


Figure 1. *The outline of case-control studies; cases with outcome A are compared with controls without outcome A, differences in antecedent exposure is compared and risk estimates are calculated.*

The results of cohort studies and case-control studies are reported as the relative risk for the disease under study in the exposed group related to the risk for the disease in the unexposed group. If the relative risk is greater than 1.0, the exposed group has a greater risk of the disease under study than the unexposed group. Risk ratio, rate ratio and odds ratio are all different measures of relative risk (Figure 2). In a cohort study one can calculate the relative risk directly from the results expressed as rate ratio or risk ratio [52]. In a case-control study this is not possible since the number of exposed or unexposed subjects in the source population is unknown, instead odds ratios are calculated [52]. Odds ratios are close estimates of the risk ratio if the disease is rare. This always applies to studies of rare ADRs. In a nested case-control study incidence density sampling can be used. In incidence density sampling, the disease-free controls are selected from within the cohort and matched with cases on the date the subject became a case. Then both cases and controls have the same time at risk. Since the cohort continues to be followed forward in time, a control can later become a case. When using the incidence sampling technique the odds ratio is assumed to be an unbiased estimate of the incidence rate ratio [53].

	Diseased	Undiseased
Exposed	A	B
Unexposed	C	D

$$\text{Risk Ratio} = \frac{\text{proportion of cases among exposed}}{\text{proportion of cases among unexposed}} = \frac{A/(A+B)}{C/(C+D)}$$

$$\text{Rate Ratio} = \frac{\text{events/person-time treated}}{\text{events/person-time untreated}} = \frac{A/PY_1}{C/PY_0} = \frac{A \times PY_0}{C \times PY_1}$$

$$\text{Odds Ratio} = \frac{\text{odds of being a case among exposed}}{\text{odds of being a case among unexposed}} = \frac{(A/B)}{(C/D)} = \frac{(A \times D)}{(C \times B)}$$

Figure 2. The relative risk equations used to calculate risk ratio and rate ratio in cohort studies and odds ratio in case-control studies.

In observational studies the investigator can only observe the effects of the exposure on the study subject. Since the investigator is not in control of allocating patients to a certain treatment like in the RCTs (*i.e.* randomly assigned treatment group), association errors might occur. Errors might be random (by chance) or systematic (biased) [47]. Random error occurs when the observed association is due to chance alone. Statistical distribution is used to estimate the random error which is quantified as confidence intervals (CI) or p-values. Bias occurs when two study groups consistently have been treated or evaluated differently [54] and may be categorised as selection bias, information bias and confounding. Selection bias occurs if recruitment of patients or losses to follow-up is related to exposure *e.g.* whether patients decide to enter or exit a study. In information bias the accuracy of the information collected on exposure and/or health status is affected by the knowledge of the outcome in a case-control

e.g. more effort might be made to find out the exposure of the cases. Confounding is another systematic error where patients with different characteristics, confounding factors, are distributed unevenly between the study groups affecting the association observed. A confounding factor has to be associated with exposure irrespective of disease and associated with the disease irrespective of the exposure. For example, differences between patients may influence the physician's choice of treatment *i.e.* confounding by indication [53, 55]. The differences in outcomes observed between the treatment groups might then be due to differences in efficacy of the treatment or differences in patient characteristics.

Bias may only be prevented by a robust study design, where cases and controls are treated alike. Confounding factors may be addressed in the study design by restriction (to those with a specific value of the confounding variable, *e.g.* smokers or non-smokers) or matching (subjects in different exposure groups have the same value of a potential confounder *e.g.* age or sex) [53]. In the data analysis, confounding factors can be addressed by stratification (analysis within categories of the confounder) or multivariate modelling (simultaneously adjusting for a number of variables to estimate the independent effect of each one) [53]. In observational studies, unmeasured confounding can be addressed by for example propensity scores or by sensitivity analyses [54]. Propensity scores are used to calculate the probability of receiving a treatment given the observed covariates for each subject. Sensitivity analyses are used to determine how strong and how imbalanced a confounder would have to be among drug categories to explain the observed effects.

In RCTs, unmeasured confounding or unknown confounders are assumed to be evenly distributed between the treatment groups through the randomisation process [47]. Differences observed are considered to be due to chance and can hence be quantified. Although RCTs are considered less vulnerable to methodological problems, RCTs may overestimate the differences between new and standard therapies since healthier patients are enrolled [47]. Violations of the study protocol can also result in biased estimates [47]. This can be dealt with using a per protocol analysis or an intention to treat analysis. In the per protocol analysis only those patients for which no protocol violations have occurred are investigated. In the intention to treat analysis the results are treated as if the patients followed the protocol accurately. The estimated effect observed in the intention to treat analysis may be underestimated compared with the true effect, but is thought to more reflect the “real life” clinical situation

Secondary data sources in pharmacoepidemiology

Pharmacoepidemiological studies usually retrospectively recreate past events using medical records, questionnaires or other registered data. To do this more efficiently many studies use secondary data sources containing medical care data that has already been collected, mainly for administrative purposes [56]. The information available in these health care databases varies between different data sources but may contain information on filled prescriptions and hospitalisations [57]. Although detailed information is available from electronic medical records they are seldom used since the information is difficult to extract and use in research. Instead researchers in the US often use insurance claims databases, where the insurance company is billed for the costs for specific services, procedures and pharmaceuticals [57].

Another data source commonly used in pharmacoepidemiology is the GPRD (the General Practice Research Database) in the UK where selected GPs (general practitioners) send in information from the medical case record on enrolled patients to a research database [58].

The main strength of using secondary data sources in pharmacoepidemiological studies is that data is collected prospectively without knowing the research question issues of bias (recall bias or interview bias), drop outs and completeness of response may be reduced [57, 59]. Moreover, data is already archived [59, 60] and it might be possible to examine delayed health effects [56]. The main disadvantage when using secondary databases is that the data is not collected to answer a specific research question. Crucial information might be lacking such as information on potential confounders like smoking and alcohol consumption [56, 58, 60].

In Sweden several health care databases are available most of which are at the National Board of Health and Welfare [61] including the Cancer Register (since 1958), the Cause of Death Register (since 1952), the Medical Birth Register and congenital malformation surveillance (since 1973), the Hospital Discharge Register (national coverage since 1987) and the Swedish Prescribed Drug Register (since July 2005) [44]. Since all of these registers include the ten-digit personal identifier unique to every Swedish citizen, the information available in these registers may be linked and it is possible to acquire more information from *e.g.* medical case records. These registers have been used in pharmacoepidemiology ever since they were established [62].

In this thesis secondary data was extracted from The Cause of Death Register, Swedish Drug Information System (SWEDIS), medical case records, the forensic computerised databases, hospital discharge registers and prescription databases as further described in the Methods section.

Two examples of drug safety issues

Warfarin and cerebral haemorrhages

Warfarin was introduced as a rodenticide in 1948 after bleeding disorders had been observed in cows eating spoiled sweet clove silage. The name, warfarin, is an acronym derived from the name of the patent holder; Wisconsin Alumni Research Foundation. The potential use of warfarin as a therapeutic agent was recognised but not widely accepted until 1951 and warfarin was approved for medical use in 1954 [63]. Warfarin affects the synthesis of clotting factors II, VII, IX and the anticoagulant proteins C and S by interfering with the vitamin K metabolism [64].

Treatment with warfarin is effective in preventing progression or recurrence of VTE, systemic embolisation in patients with prosthetic heart valves or chronic atrial fibrillation, for primary prevention of acute myocardial infarction in high-risk patients, and for the prevention of stroke, recurrent infarction, and death in patients with acute myocardial infarction [64]. However, warfarin has a narrow therapeutic window and a varying response between patients

[64]. Therefore, the effects of treatment have to be closely monitored which is done by measuring the INR (International Normalised Ratio) value. This is calculated from the patient's prothrombin time, the time it takes for a clot to form *in vitro*. The INR value should be monitored daily during the first days and then slowly reduced to every four weeks in patients with a stable INR value [64]. The therapeutic range for most clinical indications is set at a target INR value of 2.0-3.0 [64]. A higher target INR value (2.5-3.5) is recommended for patients with mechanical prosthetic heart valves and acute myocardial infarction [64]. A lower INR range (1.5-2.0) is effective in patients with VTE who have received six months of full treatment [64]. Despite the close monitoring of treatment effects bleedings are common ADRs. Bleedings occur in 7-15 patients per 100 treatment years [65-68] and major bleedings occur in 2-8 patients per 100 treatment years [65, 68-71]. Higher frequencies of bleedings have been reported during the start of treatment [72]. Of patients treated with oral anticoagulantia, intracerebral haemorrhage (ICH) occur in 0.1-0.9% [70, 73, 74], which is associated with a high mortality [75-77].

ICH are caused by an arterial rupture, followed by haematoma formation, haematoma enlargement and peri-haematoma oedema [78]. Initial clinical symptoms of ICH are symptoms of disturbed consciousness, headache, nausea/vomiting and very high blood pressure. Patients with ICH have a high fatality rate, 42% die during the first month after diagnosis and only 38% survive the first year [78]. The risk for ICH is increased in men and in elderly, in patients with hypertension, a previous cerebral ischemia and in individuals with high alcohol consumption [74, 78].

The mechanism of warfarin-related cerebral haemorrhages is to some extent unknown. Warfarin does not appear to promote vascular injury, inhibit vascular repair or induce arterial rupture, instead warfarin may unmask subclinical haemorrhages [79]. Most ICHs occur in patients with INR values within the therapeutic range. Conventional intensities of warfarin treatment increase the risk of ICH 5-10 times [79] and patients treated with warfarin have a doubled risk of fatal ICH [78]. Several risk factors for warfarin-induced cerebral haemorrhage have been proposed such as advanced age, excessive acute or chronic alcohol intake, hypertension, liver disease, diabetes mellitus, malignancy, cerebrovascular disease, poor drug compliance, bleeding tendency (including coagulation defects and thrombocytopenia), instability of INR control, INR above 3.0 [64, 68, 77, 80-82] and variation in dietary intake of vitamin K [64, 82, 83]. Concomitant use of interacting drugs may also increase the risk of adverse effects of warfarin treatment [64, 68, 80-82].

In theory, extensively albumin-bound compounds may displace warfarin and potentiate the warfarin response, since warfarin is highly bound to albumin in the circulation [64]. However, this effect is only transient and most known drug-drug interactions with warfarin occur during metabolism of warfarin. Warfarin is a racemate, and the more potent enantiomer, the S-form, is metabolised almost solely in the liver by CYP2C9 [64, 83]. Hence, drugs inhibiting the expression of CYP2C9 will decrease warfarin clearance, increase plasma levels of warfarin and increase the antithrombotic response at any given warfarin dosage. In a recent review [81] 187 separate reports of interactions involving 120 different drugs and foods that

interact with warfarin were identified. Many of the drugs identified were known inhibitors or inducers of CYP2C9 (*e.g.* fluconazole, fluvastatin, rifampin and sertraline). Patients were also using drugs known to interact with CYP1A2 (*e.g.* inhibited by quinolones) and CYP3A4 (*e.g.* inhibited by macrolides) that metabolise the R-enantiomer of warfarin [81]. Drugs might also inhibit the synthesis of vitamin K, increasing the clearance of vitamin K-dependent coagulation factors, or interfere with other pathways of haemostasis [64, 81], such as impairment of platelet function (*e.g.* by acetylsalicylic acid and NSAIDs) [83]. Of patients treated with warfarin, 54-65% are simultaneously prescribed at least one drug that may increase the INR value [82, 84, 85]. Wittkowsky *et al.* [84] found that drugs containing paracetamol and thyroid hormones were the most commonly used drugs that might increase the INR value when used in combination with warfarin.

Antipsychotic drugs and venous thromboembolism

Since the discovery of antipsychotic drugs in the early 1950's they have been used to treat symptoms of a wide range of disorders including psychoses, severe anxiety and mood disorders, behavioural disorders and dementia [86]. The pharmacodynamics of specific antipsychotics varies greatly and effects are mediated through a range of different receptors [87].

The first-generation of antipsychotic drugs (conventional antipsychotics) decrease positive symptoms of schizophrenia, *e.g.* hallucinations and delusions, but have limited effect on negative symptoms, on cognition or on mood disturbances [88]. Moreover, they fail to achieve a response in up to 30% of treated patients [87]. First-generation antipsychotic drugs are divided into low-potency antipsychotics (dosage range of 300 mg/day or greater) that are more sedative and more hypotensive than are high-potency drugs. ADRs are however common, and occur in 90% of patients treated with first-generation antipsychotic drugs, especially extrapyramidal (neurological) ADRs [87]. Use of first-generation high-potency antipsychotics has been associated with fewer cardiovascular ADRs, but a higher risk for extrapyramidal ADRs. Moreover, moderate hyperprolactinaemia is a common ADR in patients treated with first-generation antipsychotics that results in galactorrhea, amenorrhea and sexual dysfunction [87, 89].

Second-generation antipsychotic drugs (atypical antipsychotics) may have effects on both positive and negative psychotic symptoms, have lower risk for extrapyramidal ADRs and have not been associated with prolactinaemia (except for risperidone) [89]. Clozapine, the prototype drug for the second-generation antipsychotic drugs, was first synthesised in the 1960's. The effects of clozapine are mediated through dopamine receptors, histamine receptors, acetylcholine receptors, muscarine receptors and serotonin receptors [86, 88]. However, the use of clozapine has been associated with an increased risk for agranulocytosis and was in fact withdrawn from the market shortly after introduction in the 1970's [87]. This potentially fatal ADR has limited the use of clozapine to patients who have failed to respond adequately to first-generation antipsychotic drugs or who experience extrapyramidal ADRs. Treatment with second-generation antipsychotic drugs has also been associated with worsening of cardiovascular risk factors such as weight gain, hyperglycemia and

hyperlipidemia [86, 88, 90-92]. Moreover, during recent years treatment with antipsychotic drugs has been associated with an increased risk for VTE [93-100], suggesting a possible causal link. These studies are summarised in Table 2. There is no obvious explanation known today for the increased risk of VTE in users of antipsychotic drugs. However, in users of antipsychotic drugs, several risk factors for VTE are present which are associated with the disease or the antipsychotic drug treatment.

VTE start with the formation of a venous clot (thrombosis) in any section of the venous system, often in the deep veins of the legs (DVT, deep vein thrombosis). The clotting process is initiated by damaged vessel walls, alterations in the flow and hypercoaguability of the blood (Virchow's triad, 1856). Pulmonary embolism (PE) occurs if part or all of a thrombus is dislodged from a vein wall, travels to the lungs and lodges within the pulmonary arteries. VTE occurs in the population in about 0.5-1 individual per 1000 individuals per year [101, 102], with a fatality rate of 1-10% [102, 103], mainly due to PE. VTE is a multicausal disease [101, 103] and two-thirds of first time DVTs are due to known risk factors [101] that can be traced back to the three main causes of thrombi formation stated by Virchow. In a recent case-control study [104], fractures and surgery were strong risk factors for VTE (odds ratio of 25 and 35, respectively). Other risk factors associated with VTE were a recent contact with health care, overweight, co-morbid conditions (*e.g.* varicose veins, inflammatory bowel disease and cancer), pregnancies and patients treated with female hormones or NSAIDs. Other established risk factors for VTE are age (one of the strongest risk factors), immobilisation, injuries, antibodies against cardiolipin or lupus anticoagulants, inherited risk factors (*e.g.* mutations in the genes coding for Factor V and Factor II) and hyperhomocysteinemia [101, 103].

Table 2. A summary of the most recent studies on the risk for venous thromboembolism in users of antipsychotic drugs.

Study	Time period	Age (years)	Study design	Study subjects	Events	Number of cases	Result, relative risk (95% CI)
Walker <i>et al.</i> [93]	1991-1993	10-54	Record linkage study	67 072 current and former users of clozapine. US	Mortality, including PE	18 cases of PE currently using clozapine and 1 case of PE in former users of clozapine.	Clozapine RR: 5.2 (no CI given)
Zornberg <i>et al.</i> [94]	1990-1998	<60	Nested case-control study	29 952 users of AP. UK	VTE	14 of 42 cases of VTE in patients currently using FGA; 11 of 168 in controls were currently using AP.	FGA AOR: 7.1 (2.3-22.0) Low-potency FGA AOR: 24.1 (3.3-172.7) High-potency FGA AOR: 3.3 (0.8-13.2) FGA AOR: 9.7 (2.3-40.9) Low-potency FGA AOR: 29.3 (2.8-308.2)
Parkin <i>et al.</i> [95]	1990-1998	15-59	Case-control study	75 subjects with fatal PE and 300 GP controls. New Zealand	PE	9 cases of PE were exposed to AP and of these 7 were exposed to low-potency FGA.	SGA AHR: 2.01 (1.50-2.70) FGA AHR: 1.02 (0.67-1.55) >1 AP AHR: 4.80 (2.29-10.10) AP AHR: 1.10 (0.95-1.27) Haloperidol AHR: 1.43 (1.18-1.74)
Liperoti <i>et al.</i> [96]	1998-1999	≥65	Retrospective cohort study	19 940 new users of antipsychotic drugs and 112 078 non-users. US	VTE	64 cases of VTE in 11 613 users of SGA, 28 cases of VTE in 7 652 users of FGA. No cases of VTE in 675 users of more than one AP.	AP AOR: 10.49 (3.95-27.85)
Ray <i>et al.</i> [97]	1994-2000	≥65	Retrospective cohort study	Individuals prescribed 22 514 AP, 75 0649 AD, 33 033 TH. Canada	VTE	19.2 cases of VTE per 1000 person-years exposed to AP, compared with 12.0 cases of VTE per 1000 person-years exposed to TH and 14.3 cases of VTE per 1000 person-years exposed to AD.	AP AOR: 10.49 (3.95-27.85)
Hamanaka <i>et al.</i> [98]	1998-2002	NR	Retrospective prevalence study with a control group	1 125 medico-legal autopsy cases. Japan	PE	8 of 34 cases of fatal PE were using AP.	AP AOR: 10.49 (3.95-27.85)
Masopust <i>et al.</i> [99]	1996-2004	18-60	Case-control study	266 cases 274 controls with arterial hypertension. Czech Republic	VTE	13 cases of VTE and 5 controls used AP.	AP OR: 2.76 (1.01-7.55)
Lacut <i>et al.</i> [100]	2000-2004	>18	Case-control study	677 cases and 677 controls. France	VTE	Among the cases 46 were exposed to FGA and 10 were exposed to SGA. Among the controls 15 were exposed to FGA and 4 to SGA.	AP OR: 3.5 (2.0-6.2) FGA OR: 4.1 (2.1-8.2) SGA OR: 2.7 (0.7-10.0)

*Excluding nursing home residents with a diagnosis of schizophrenia.

Abbreviations: AD, antidepressant drugs; AHR, adjusted hazard ratio; AOR, adjusted odds ratio; AP, any antipsychotic drugs; CI, confidence interval; FGA, first-generation antipsychotic drugs; GP, general practitioner; NR, not recorded; OR, odds ratio; PE, pulmonary embolism; RR, relative risk; SGA, second-generation antipsychotic drugs; TH, thyroid hormones; VTE, venous thromboembolism.

Aims of the thesis

The general aim of this thesis was to describe patterns of pharmaceutical drug use related to morbidity and mortality and to investigate two serious adverse drug reactions concerning risk factors and predisposing factors.

Specific aims were:

- I To determine the proportion of fatal adverse drug reactions and fatal drug intoxications in a Swedish population.
- II To describe the panorama of drugs causing (or associated with) fatal intoxications in Sweden.
- III To evaluate the frequency, severity and preventability of warfarin-induced cerebral haemorrhages due to warfarin-drug interactions.
- IV To examine the risk for venous thromboembolism among users of antipsychotics.
- V To investigate if the suggested increased risk for fatal pulmonary embolism among subjects treated with antipsychotics can be shown in a Swedish medico-legal autopsy series.

Methods

The papers included in this thesis have investigated drug-related morbidity and mortality using different pharmacoepidemiological study designs (Table 3). In Paper I the Cause of Death Register was used as a sampling frame to describe a series of suspected FADRs. The forensic pathology and forensic toxicology databases were used in Paper II to identify and describe a series of subjects with a fatal intoxication. These databases were also used in Paper V to estimate the risk of fatal PE in users of antipsychotic drugs using a case-control study design. Hospital discharge registers were used in Paper III to identify and describe a series of patients with a diagnosis of cerebral haemorrhage. Danish hospital discharge registers were used in Paper IV to identify cases with a diagnosis of VTE and the risk of VTE was estimated using a nested case-control study design.

Table 3. *An overview of study subjects included and the methods used in this thesis.*

Paper	Study period (year)	Included study subjects	Number of study subjects	Secondary data resources used*	Study design
I	2001	Fatalities in a Swedish population	1 574	The Cause of Death Register, medical case records, SWEDIS	Case series
II	1992-2002, 2005	Deceased with intoxication as the cause of death	6 998, 426	The forensic pathology and forensic toxicology databases	Case series
III	2000-2002	Patients with a discharge diagnosis of cerebral haemorrhage	621	Hospital discharge registers	Case series
IV	1997-2005	Patients with a discharge diagnosis of VTE and population based controls	65 989	The prescription registers, discharge registers and the civil registration system, Denmark	Nested case-control study
V	1992-2005	Deceased with PE as the cause of death and deceased controls	14 439	The forensic pathology and forensic toxicology databases	Case-control study

*Swedish registers unless otherwise noted.

Abbreviations: PE, pulmonary embolism; SWEDIS, Swedish drug information system; VTE, venous thromboembolism.

The Cause of Death Register (Paper I)

The Cause of Death Register, held by the National Board of Health and Welfare, Sweden, was established in 1961 [61]. When a person dies the cause of death has to be established by the treating physician and a death certificate has to be written, signed and sent to the National Board of Health and Welfare for registration in the Cause of Death Register. Among other things, information about the deceased (including a ten-digit personal identifier, unique to every Swedish citizen), the underlying cause of death, manner of death, place of death and whether an autopsy was performed is registered. In Paper I, every seventh deceased in 2001 was randomly selected in three counties in southeast Sweden, Östergötland County, Jönköping County and Kalmar County, based on information in the Cause of Death Register (n=1574). Additional information (*e.g.* medical case records and medico-legal files) was retrieved and scrutinised to assess whether a suspected ADR could have caused or contributed to the cause of death in these individuals.

The Swedish drug information system (Papers I, III)

SWEDIS was set up as a pilot project in 1965 and was established in 1971 [62]. Since 1975 it has been compulsory for health care professionals authorised to prescribe drugs to report all suspected ADRs for new drugs (except those labelled as common in the summary of product characteristics) and serious ADRs for all drugs to the Medical Products Agency (MPA) in Sweden [62]. Since 2007 all nurses may report suspected ADRs to the MPA [105]. In Sweden six regional centres evaluate the spontaneously reported ADRs within their region and assess whether the suspected ADR may be related to the drug treatment [1]. Information from each report about the patient, suspected drugs, suspected ADRs, co-morbidities, outcome, causality assessment and administrative data is entered in the national database on ADRs, SWEDIS. About 4000 ADRs are spontaneously reported to the MPA each year and of these approximately 100 ADRs are fatal [106]. In Paper I and Paper III information from SWEDIS was used to ascertain whether the suspected ADRs found had been reported to the MPA.

The forensic pathology and forensic toxicology databases (Papers II, V)

Information on fatalities are not only available in the Cause of Death Register, but also in the registers within the National Board of Forensic Medicine, *i.e.* the forensic pathology and forensic toxicology databases, where information on all medico-legal autopsies performed since 1992 are registered [107] covering the entire Swedish population. Besides information on cause and manner of death, information on pharmaceutical substances, alcohol and illicit drugs detected *postmortem* and the ten-digit personal identifier is available in these databases. According to Swedish regulations, all certified or suspected unnatural deaths - including cases with certified or suspected substance abuse, unknown cause of death, unknown identity or suspected malpractice cases - must be reported to the police by the physician issuing the death certificate. In most of these cases, the police will request a forensic autopsy. Approximately 5000 forensic autopsies (about 5% of all fatalities) are carried out in Sweden each year. During autopsy, femoral blood, urine and vitreous humour samples are collected, fluorinated, and submitted to the Department of Forensic Toxicology and Genetics, the National Board of Forensic Medicine, Linköping, which constitutes a national laboratory where samples

routinely are screened for pharmaceutical drugs and ethanol. Illicit drugs are only screened for upon request by the responsible pathologist, *i.e.* when an intake seems likely, based on circumstantial information and autopsy findings. In Paper II and Paper V cases were selected from the forensic toxicology and forensic pathology databases based on the international classification of diseases, 9th revision (ICD-9) codes linked with the cause of death diagnoses made by the pathologist.

In Paper II all suicides, uncertain cases and accidents where the cause of death was a fatal intoxication (ICD-9: E950, E980 and E859) during the period 1992-2002 were identified. Substances detected in more than 50 individuals were recorded. In this thesis individuals with a fatal intoxication in the year 2005 are included as well. Moreover, the presentation in this thesis is focused on substances detected in more than 200 individuals. The number of subjects where each substance had been detected was recorded as well as the number of subjects where the substance was detected in concentrations above a cut-off limit. The concentration where the cut-off limit was set for each substance was based on a Swedish compilation of fatal and non-fatal concentrations of drugs in *postmortem* femoral blood [108]. In that compilation cases where forensic toxicology analyses had been performed were divided into four groups; cases with a fatal intoxication due to one drug, cases with a fatal intoxication due to one drug in combination with other drugs and/or ethanol, cases with other causes of death without incapacitation due to drugs and suspected drugged drivers. For each category of cases the detected concentrations (median and range; 10th percentile and 90th percentile) for each drug were noted. In Paper II, the cut-off limit for each substance was set at the highest concentration (90th percentile) detected among cases with other causes of death without incapacitation due to drugs. For ethanol, the cut-off value was based on a recent compilation of *postmortem* blood-ethanol concentrations found in the Swedish forensic material [109]: the lowest concentrations (5th percentile) where ethanol was detected in acute intoxications deaths (2200 µg/g). Carbon monoxide and endogenous substances also registered in the databases were excluded in Paper II. No cut-off concentrations were set for illicit drugs due to inter-individual differences in tolerability or for diazepam since only a few deaths have been associated with this drug [110]. Due to the significant *postmortem* degradation of clonazepam, flunitrazepam, nitrazepam and propiomazine [111], the number of cases where their metabolites were detected were noted instead of the parent drug. Moreover, amitriptyline, citalopram, diazepam, flunitrazepam, propiomazine, propoxyphene, tramadol, venlafaxine, zolpidem and zopiclone were selected to study changes over time. In this thesis changes over time, 1997-2006, are shown for tramadol and propoxyphene since these drugs are opioids analgesics used to treat moderate to severe pain.

In Paper V medico-legal autopsy cases aged 18-65 were selected. Subjects with intoxication (ICD-9: 800-999, except 995.2) and other external causes of death (ICD-9: E800-E929, E950-E999) were excluded. All subjects where PE (ICD-9: 415.2) was the cause of death were identified. Deceased without PE as the cause of death were considered controls. Use of antipsychotic drugs was based on the results of the *postmortem* analyses and categorised as first-generation high-potency antipsychotic users (flupenthixol, fluphenazine, haloperidol, perphenazine, pimozide, trifluoperazine, and zuclopenthixol), first-generation low-potency

antipsychotic users (chlorpromazine, chlorprothixene, dixyrazine, levomepromazine, melperone, and thioridazine), second-generation antipsychotic users (clozapine, olanzapine, risperidone, quetiapine and ziprasidone) and non-users. Since subjects may be using antipsychotics from more than one category, we classified all subjects in whom a second-generation antipsychotic drug was detected as users of second-generation antipsychotics, and all subjects in whom a first-generation low-potency antipsychotic drug was detected, in the absence of a second-generation antipsychotic drug, as users of first-generation low-potency antipsychotics. If no antipsychotic drug was detected the subject was classified as a non-user. The entire medico-legal dossier was examined in subjects where antipsychotic drugs were detected *postmortem* and where PE was the cause of death to identify possible risk factors for VTE [112].

Hospital discharge registers (Papers III, IV)

The Swedish Hospital Discharge Register, kept by the National Board of Health and Welfare, has information on all discharges since 1987 [61]. Information about the patient, the hospital, administrative data and medical data is registered in local administrative patient registers. Data from these registers is sent to the National Board of Health and Welfare and stored in the Hospital Discharge Register. The medical data contain information on up to eight discharge diagnoses coded using the ICD-9 codes until 1996 and ICD-10 codes thereafter [113]. In Paper III the administrative patient registers at four hospital departments (the Department of Neurology and the Department of Neurosurgery, Linköping University Hospital, the Department of Internal Medicine, Norrköping Hospital and the Department of Internal Medicine, Motala Hospital), were used to identify patients diagnosed with cerebral haemorrhage (ICD-10 codes: I.60, I.61, I.62). Medical case records were retrieved and scrutinised to assess whether treatment with warfarin could have contributed to the cerebral haemorrhage in these patients.

The national register on dispensed pharmaceuticals in Sweden, the Swedish Prescribed Drug Register, was introduced in 2005 [44]. There is not yet enough information available in this register to examine the risk for VTE in users of antipsychotic drugs using a case-control study design. We therefore turned to Denmark where similar registers have been available since 1989 (North Jutland County) and 1996 (Aarhus County). As in Sweden, unambiguous linkage between various registers can be performed in Denmark using the civil registry number [114]. The civil registry number is given at birth and is unique to each Danish citizen and the civil registry system retains data on vital status, address, and emigration for the Danish population since 1968 [114]. In Denmark, hospital discharge registers retain data on all discharges from all non-psychiatric hospitals since 1977 [115]. The files include information on the civil registry number, dates of admission and discharge, and up to 20 discharge diagnoses and procedures, coded according to ICD-8, until end of 1993 and ICD-10 thereafter.

In Paper IV, patients with a first diagnosis of a VTE (DVT: ICD-8 codes: 451.00 and ICD-10 codes: I80.1, I80.2, I80.3, and PE: ICD-8 codes: 450.99 and ICD-10 codes: I26) were identified in the hospital discharge registers in the counties of Aarhus and North Jutland. In a second analysis that focused on patients with a primary (unprovoked) VTE, patients with

classic predisposing conditions [116] (surgery, major trauma, fractures or pregnancy during the three months before the diagnosis of VTE as well as pre-existing cancer and a cancer diagnosis within three months after the VTE) were excluded. To control for the increased risk of VTE observed in immobilised patients [103], patients whose VTE was a secondary (*i.e.* not first listed) diagnosis for the admission were excluded. Using the civil registry system we aimed to select 10 population controls for each case matched on age, sex and county. The controls were assigned an index date identical to the VTE admission date for the case. Moreover, data on myocardial infarction, stroke, peripheral arteriosclerosis in the legs, heart failure and diabetes mellitus was collected from the discharge registers since these diseases might increase the risk of VTE [103]. Only diagnoses before the admission date/index date were included.

Drug prescription registers (Paper IV)

The pharmacies that serve North Jutland County and Aarhus County are equipped with electronic accounting systems that are primarily used to secure reimbursement (cost of prescribed medications) from the National Health Service [115]. For each filled prescription, the customer's civil registry number, the type and amount of drug prescribed according to the anatomical therapeutic chemical (ATC) classification system, and date of dispensing of the drug is transferred from the pharmacies to the prescription databases.

In Paper IV, data on all prescriptions for antipsychotic drugs filled by cases and controls within 365 days before the date of hospital admission of VTE (cases) or the index date (controls) was obtained from the population based prescription databases of North Jutland and Aarhus counties. Use of antipsychotics was classified as use of first-generation low-potency antipsychotics (chlorpromazine, chlorprotixene, melperone, pipamperone, promazine, and thioridazine), use of first-generation high-potency antipsychotics (flupenthixol, fluphenazine, haloperidol, penfluridol, periciazine, perphenazine, pimozide and zuclopenthixol) and use of second-generation antipsychotics (amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, sulphiride and ziprasidone). The individuals were further classified according to their most recent use as: current users (having filled at least one prescription within 90 days before admission for VTE or index date for controls), recent users (absence of recorded prescription within 90 days before admission/index date and having filled at least one prescription within 91-180 days before admission/index date), former users (absence of recorded prescription within 180 days before admission/index date and having filled at least one prescription within 181-365 days before admission/index date), or non-users (absence of recorded prescription for any antipsychotics within 365 days before admission/index date). From the prescription databases, we also ascertained current use of statins, low dose acetylsalicylic acid, postmenopausal hormone replacement therapy (HRT) and vitamin K antagonists since these drugs might affect the risk for VTE [102, 117-120]. We also retrieved data regarding "ever use" of oral hypoglycemic agents and insulin, as a marker of diabetes mellitus [101].

Clinical assessment of adverse drug reactions and intoxications (Papers I, III)

In Paper I death certificates and additional case records (hospitals and/or primary care centres and medico-legal files) and case information from SWEDIS were scrutinised in a stepwise manner. The first examination was performed by health care professionals specially trained in ADRs focusing on pharmacological treatment, clinical course of outcome and laboratory and/or autopsy findings. We focused on the pharmacological treatment two weeks preceding death and drugs used for palliation were not classified as suspected FADRs. Second, a first assessment as to whether the death was due to a FADR or drug intoxication was performed by two pharmacists and one clinical pharmacologist. The possible FADRs and intoxications identified in the first assessment were re-evaluated by two specialists in clinical pharmacology and forensic pathology. In order for an event to be classified as a suspected FADR or drug intoxication, consensus had to be reached between all assessors. To validate the methodology used, one out of every ten fatalities not categorised as a FADR or drug intoxication was selected at random and scrutinised again. The fatal suspected drug intoxications were excluded in Paper I but are still included in this thesis.

In Paper III, case records were scrutinised and relevant clinical information was noted in a standardised form including date of birth, sex, diagnosis, history of head trauma, concomitant drug use and INR measurements. Patients treated with warfarin at the onset of symptoms were identified. Potential drug interactions were identified based on the Swedish Drug Compendium (FASS) [121] where warfarin-drug interactions classified as category C or D were included. Class C: The interaction may cause altered drug effects or cause ADRs, but these might be controlled with individual dosing and/or measurements of drug concentrations in plasma. Class D: The interaction might have clinically important consequences with severe ADRs or no drug effect, or the drug effects are difficult to control with individual dosing and the combination should be avoided. In addition, some obvious pharmacodynamic interactions were included since the information in the Swedish Drug Compendium (FASS) is focused on pharmacokinetic interactions and additive effects are not indicated. The information retrieved from the patients' case records was assessed by a group of experts in clinical pharmacology. Causality between the warfarin treatment and cerebral haemorrhage as well as avoidability of the ADR was determined.

Causality assessment of adverse drug reactions (Papers I, III)

Causality between the drugs suspected to be associated with a suspected ADR was assessed in Paper I and Paper III. The causality was assessed, on the basis of the available information, according to the WHO definitions [1]; *Certain*: plausible time relationship to drug exposure, positive dechallenge and rechallenge. *Probable*: reasonable time sequence to drug exposure, positive dechallenge, other explanations are unlikely. *Possible*: reasonable time sequence to drug exposure, possible lack of dechallenge, other possible explanations may exist. *Unlikely*: unreasonable time sequence to drug exposure and other plausible explanations exist. *Unclassified*: more data is needed for a proper assessment or additional data is being examined. *Unclassifiable*: insufficient or contradictory information that cannot be

supplemented or verified. In Paper I and Paper III, a suspected ADR was defined as having a causality assessed at a level of at least “possible” (*i.e.* possible, probable or certain).

Assessment of avoidability of adverse drug reactions (Paper III)

Avoidability was assessed in Paper III with a focus on warfarin-drug interactions. The avoidability of ADRs was assessed, on the basis of available information, according to criteria set up by Hallas *et al.* [122]; *Definitely avoidable*: the drug event was due to a drug treatment procedure inconsistent with present-day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account. *Possibly avoidable*: the prescription was not erroneous, but the drug event could have been avoided by an effort exceeding the obligatory demands. *Not avoidable*: the drug event could not have been avoided by any reasonable means, or it was an unpredictable event in the course of a treatment fully in accordance with good medical practice. *Unevaluable*: the data for rating could not be obtained or the evidence was conflicting.

Drug utilisation (Papers II, III)

The use of drugs was estimated by their sales retrieved from the National Corporation of Pharmacies, Stockholm, Sweden (Apoteket AB) described here as the number of DDD per 1000 inhabitants per day. In Paper II the amount of drugs sold to the pharmacies (wholesale statistics) were retrieved for the substances most commonly detected among the deceased with a fatal intoxication (citalopram, nitrazepam, paracetamol, propiomazine, propoxyphene and zopiclone). A fatality ratio was calculated by relating the number of cases where the substance might have contributed to the intoxication with the number of DDDs sold of that substance. In Paper III statistics on the amount of warfarin sold by the pharmacies (retail statistics) was retrieved and the incidence of warfarin-related haemorrhages was calculated.

Analytical methods (Papers II, V)

At the Department of Forensic Toxicology and Forensic Genetics, National Board of Forensic Medicine, Linköping, pharmaceutical drugs were analysed by gas chromatography with nitrogen specific detector after alkaline and neutral extraction with butyl acetate [108]. This method covers about 200 different substances that may be implicated in fatalities in Sweden. Ethanol was analysed with head-space gas chromatography [123]. Certain pharmaceutical drugs (*e.g.* some antipsychotics) and illicit drugs were analysed upon request by the responsible pathologist, when an intake seemed likely based on circumstantial information and autopsy findings. The antipsychotic drugs not included in the screening process were analysed as follows: Flupenthixol, fluphenazine, perphenazine, trifluoperazine and zuclopenthixol were analysed by gas chromatography with nitrogen specific detector after alkaline extraction; Risperidone and ziprasidone were analysed by liquid chromatography-triple quadruple mass spectrometry (LC-MS-MS) after alkaline extraction [124]; Pimozide was analysed by high performance liquid chromatography (HPLC) after alkaline extraction. Illicit drugs were screened in urine, if available, or in blood, by immunoassays. All positive screening results were confirmed and quantified by analysing blood with gas chromatography-mass spectrometry (GC-MS) using single ion monitoring [125, 126].

Statistical methods (Papers I-V)

For comparisons, Chi-square tests were used for dichotomous variables (Papers I, II, III, V), the Student's t-test for continuous variables (Paper III), and Mann-Whitney tests for non-parametric comparisons (Paper V). Logistic regression analyses were performed (Papers IV, V) to compute relative risk estimates (odds ratios) with 95% CI associated with VTE and fatal PE, respectively and the use of antipsychotic drugs. In Paper IV the logistic regression analyses were adjusted for discharge diagnoses of myocardial infarction, stroke, peripheral arteriosclerosis in the legs, heart failure, diabetes mellitus and current use of statins, low dose acetylsalicylic acid, postmenopausal HRT and vitamin K antagonists. In Paper V, logistic regression analyses were adjusted for age (continuous variable) and sex.

Results

Fatal adverse drug reactions (Paper I)

Pharmaceutical drugs were suspected to be associated with FADRs in 3.1% (49/1574; 95% CI: 2.2-4.0%) of the total study population and in 6.4% (41/639; 95% CI: 4.5-8.3%) of those who died in hospital. The deceased included in Paper I had a median age of 81 years (range: 0-104 years) at the time of death. Information on drug use was available in 1553 subjects (99%) and most of the study subjects were using several drugs two weeks preceding death (median of 7 drugs; range: 0-28 drugs).

Haemorrhage was the most common FADR (36 cases) followed by cardiovascular disorders (5 cases). In total, 33 different substances were suspected to be implicated in the 49 FADRs and in 19 cases (39%), more than one substance was suspected to have caused the FADR. Antithrombotic agents (16 cases) and platelet aggregation inhibitors (21 cases) were the drug groups most commonly implicated in subjects with FADRs (Table 4).

An ADR was mentioned on 8 death certificates (0.5%) as the underlying cause of death. The drugs mentioned on the death certificates were: clonazepam, clozapine, flucloxacillin, prednisolone, warfarin and a combination of acetylsalicylic acid, alteplase, dipyridamole and heparin. Moreover, only one of the suspected FADRs identified in the present study (2%) had been reported to the MPA as a suspected ADR. This report concerned a subject who developed cardiomyopathy during treatment with clozapine.

Fatal intoxications (Papers I, II)

In Paper I it was found that a fatal suspected intoxication could have caused or contributed to the fatal outcome in 0.6% (9/1574; 95% CI: 0.2-1.0%) of the deceased in a general Swedish population. Based on information from the death certificates, the incidence of drug intoxications in the study population was 0.7% (11/1574). Three cases stated as drug intoxications in the death certificates were excluded from the present study due to uncertainty as to whether the drug intake actually had contributed to the fatal outcome.

Table 4. *Drugs and fatal adverse drug reactions in the 49 subjects. (Paper I)*

Drug Group (ATC code)	Number of deaths (%)*	Suspected drugs, 33 in total	ADRs, 17 in total
Antithrombotic agents (B01) [†]	16 (33)	Warfarin (8), dalteparin (7), heparin (2), alteplase (1), enoxaparin (1), tenecteplase (1)	CNS haemorrhages (8), GI haemorrhages (5), intraabdominal haemorrhages (2), intravesical haemorrhage (1)
Platelet aggregation inhibitors excluding heparin (B01AC)	21 (43)	Acetylsalicylic acid (20), dipyridamole (3), acetylsalicylic acid + dipyridamole (1), clopidogrel (1)	GI haemorrhages (10), CNS haemorrhages (8), intraabdominal haemorrhages (2), respiratory tract haemorrhage (1)
Non-steroid anti-inflammatory drugs, NSAIDs (M01A)	9 (18)	Celecoxib (2), diclofenac (2), naproxen (2), rofecoxib (2), indomethacin (1), ketoprofen (1)	GI haemorrhages (4), renal dysfunction (2), CNS haemorrhages (2), cardiac failure (1)
Antidepressants (N06A)	7 (14)	Citalopram (6), sertraline (1)	GI haemorrhages (4), CNS haemorrhage (1), intraabdominal haemorrhage (1), respiratory tract haemorrhage (1)
Cardiovascular system (C)	4 (8)	Amiloride + hydrochlorothiazide (1), enalapril (1), losartan (1), propranolol (1), spironolactone (1)	Hyperkalaemia (2), agranulocytosis (1), bradycardia (1)
Antipsychotic agents (N05)	2 (4)	Clozapine (1), olanzapine (1)	Cardiomyopathy (1), grand mal convulsions (1)
Corticoids for systemic use (H02)	2 (4)	Prednisolone (2)	Cystitis (1), GI haemorrhage (1)
Antiepileptics (N03)	1 (2)	Clonazepam (1)	Grand mal convulsion (1)
Drugs used in diabetes (A10)	1 (2)	Glibenclamid (1)	Agranulocytosis (1)
Mineral supplements (A12)	1 (2)	Potassium chloride (1)	Hyperkalaemia (1)
Sex hormones (G03)	1 (2)	Oestrogen + norethisterone (1)	Pulmonary embolism (1)
Antibacterials for systemic use (J01)	1 (2)	Flucloxacillin (1)	Colitis pseudomembranous (1)
Anesthetics (N01)	1 (2)	Bupivacaine (1)	Hypotension (1)

*More than one drug could be suspected to have contributed to one adverse drug reaction.

[†]Excluding platelet aggregation inhibitors (B01AC).

Abbreviations: ADRs, adverse drug reactions; ATC, anatomical therapeutic chemical classification system; CNS, central nervous system; GI, gastrointestinal.

Hence, all but one of the suspected fatal intoxications, and three additional cases, were stated as such on the death certificates. Note that one of the subjects with a fatal intoxication (unintentional digoxin overdose) also had a suspected FADR (warfarin-related haemorrhage). The subjects who died due to intoxication were younger than the deceased subjects with suspected FADRs (67% below the age of 70 compared with 16% among the subjects with a FADR, $p < 0.01$) and were autopsied significantly more often than subjects with a suspected FADR (78% vs. 4%, $p < 0.001$). Ten different substances were implicated in these subjects; the most common drug groups were antipsychotics (4/9, 44%), antihistamines (3/9, 33%) and analgesics (2/9, 22%) (Table 5).

Table 5. *Characteristics of the 9 fatal suspected drug intoxications. (Paper I)*

Type of drug intoxication	Number of deaths (%)	Sex M/F	Median age (range)	Suspected drugs (n=10)*
Intentional	4 (44)	1/3	30 (26-81)	Nitrazepam (1), levomepromazine (1), morphine (1), nitrazepam + carbamazepine + propoxyphene + promethazine (1)
Unintentional	3 (33)	2/1	64 (53-85)	Alimemazine (1), amitriptyline (1), digoxin (1)
Unknown intent	2 (22)	2/0	66 (53, 80)	Diazepam (1), alimemazine (1)

*More than one drug could be suspected to have contributed to the drug intoxication.

Abbreviations: F, females; M, males.

The deceased subjects with a fatal intoxication in Swedish medico-legal autopsies (n=6998) included in Paper II were also “young”, with a median age of 45 years (range 0-100 years of age). The subjects who committed suicide were equally distributed between males and females whereas males dominated among the fatalities categorised as uncertain cases and accidents. Most of the deceased had taken more than one substance preceding death (median of 4 different substances were detected per case). Antidepressants, analgesics and sedatives were commonly detected drug classes. The drugs most commonly detected are listed in Table 6. Ethanol was the most commonly detected substance, however concentrations of ethanol above the cut-off value were only detected in 32% of the subjects. In contrast, in subjects where propoxyphene was detected, the most commonly detected *pharmaceutical* substance, concentrations were above the cut-off value in 73% of the subjects. Moreover, the number of cases where propoxyphene was detected increased until 1997 which was followed by a decrease (Figure 3). Simultaneously, the number of cases where tramadol was detected increased. The most commonly detected substances were detected in similar proportions in subjects with a fatal intoxication in 2005 compared with 1992-2002. However, the proportion of subjects where hydroxyzine were detected above the cut-off concentration increased (61%; 23/426 in 1992-2002 vs. 34%; 108/6998 in 2005).

Table 6. *The distribution of substances detected in more than 200 individuals with a fatal intoxication during 1992-2002 and 2005, in Sweden, and the proportion among these with concentrations above the cut-off concentration. (Paper II)*

Substance	Fatal intoxications in total 1992-2002, n=6998 (proportion above the cut-off value)	Fatal intoxications in total 2005, n=426 (proportion above the cut-off value)	Cut-off concentrations (µg/g femoral blood)
Ethanol	3341 (32%)	43 (47%)	2200
Propoxyphene	2011 (73%)	66 (73%)	0.8
Paracetamol	1761 (43%)	103 (34%)	50
Diazepam [†]	1163	68	-
7-amino-flunitrazepam [*]	1051 (39%)	28 (36%)	0.12
Morphine [†]	954	77	-
Codeine	927 (22%)	74 (24%)	0.4
Dihydropropiomazine [*]	870 (57%)	77 (48%)	0.2
7-amino-nitrazepam [*]	590 (52%)	32 (56%)	0.2
Citalopram	574 (39%)	55 (31%)	1.1
Zopiclone	564 (54%)	74 (63%)	0.4
Alimemazine	419 (45%)	55 (31%)	0.4
Amitriptyline	350 (63%)	20 (55%)	0.6
Carbamazepine	330 (24%)	14 (29%)	10
Carisoprodol	290 (64%)	14 (64%)	1.8
Levomepromazine	275 (13%)	21 (10%)	1.7
Clomipramine	261 (66%)	14 (71%)	0.4
Tetrahydrocannabinol [†]	246	27	-
Amphetamine [†]	225	27	-
Zolpidem	218 (33%)	40 (48%)	0.12
Oxazepam	217 (41%)	17 (71%)	0.7

*The number of cases where each substance was detected is represented by the number of cases where the metabolite was detected.

[†]No cut-off toxic concentration was set.

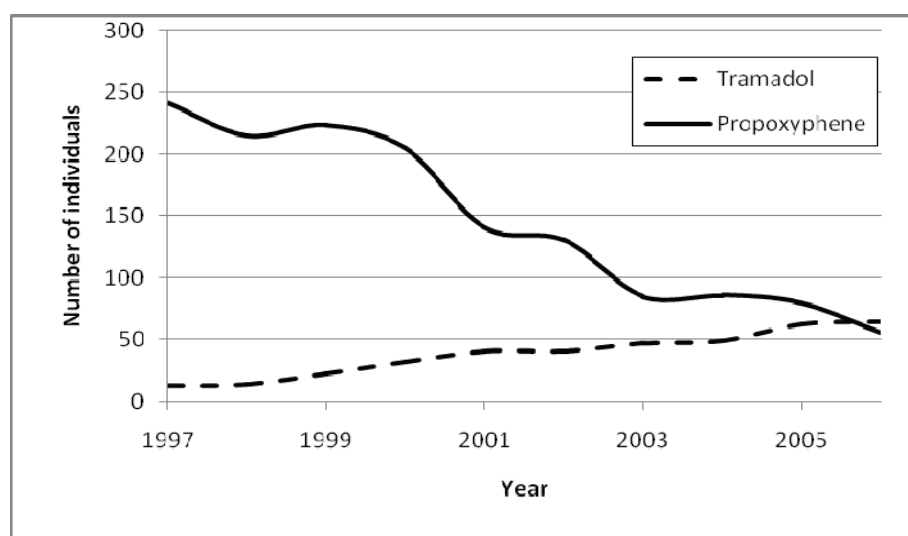


Figure 1. *Number of individuals with a fatal intoxication where propoxyphene and tramadol were detected. (Paper II)*

Warfarin-related cerebral haemorrhage (Paper III)

In Paper III medical case records were available for 96% (593/621) of the identified patients with a diagnosis of cerebral haemorrhage. It was found that 10% (59/593) of the patients with cerebral haemorrhage were treated with warfarin at onset of symptoms. Warfarin was considered to have caused or contributed to the cerebral haemorrhage in all of these cases. Two (3%) of the suspected ADRs were reported to the MPA. The patients treated with warfarin were older (median age of 77 years, range: 43-94 years *vs.* median age of 70 years, range: 12-95 years, $p < 0.01$) and were using more drugs (5 drugs *vs.* 2 drugs) than the subjects not treated with warfarin. Moreover, more subjects treated with warfarin died compared with those not treated with warfarin (44%; 26/59 *vs.* 25%; 136/534, $p < 0.01$).

The INR value at admission to hospital exceeded 3.0 in 34% (20/59) of the patients treated with warfarin and in 42% (11/26) of the deceased patients. In 5% (3/59) of the patients treated with warfarin the INR value at admission exceeded 5.0 and in 8% (2/26) of the deceased patients. A warfarin-drug interaction could have contributed to the cerebral haemorrhage in 41% (24/59). The haemorrhage was considered possibly avoidable in 12% (7/59) (Table 7). In 11% (6/59) the haemorrhage was considered not avoidable (patients treated with dalteparin, acetylsalicylic acid and tinzaparin), whereas in 19% (11/59), the unevaluable (patients treated with dipyridamole, citalopram, sertraline and paroxetine). None of the cases were classified as definitely avoidable.

Antipsychotics and risk for venous thromboembolism (Papers IV, V)

In Paper IV, compared with non-users, an increased risk of VTE was observed in current users of antipsychotics (adjusted relative risk [ARR]: 2.0, 95% CI: 1.7-2.3) (Table 8). When analysing subgroups of antipsychotic users, an increased risk of VTE was observed in current users of: first-generation high-potency, first-generation low-potency and second-generation antipsychotic drugs (ARR 1.8, 95% CI: 1.4-2.2, ARR 2.2, 95% CI: 1.6-3.0 and ARR 2.5, 95% CI: 1.9-3.3, respectively). However, an elevated risk was also observed for former users of any antipsychotic drugs (ARR: 1.6, 95% CI: 1.1-2.5). In an analysis restricted to 3471 patients with unprovoked VTE and 34 608 population based controls similar relative risk estimates were found.

In Paper V, PE was the cause of death in 279 subjects (1.9%). Antipsychotics were used at the time of death in 538 subjects (3.7%), whereof 390 were categorised as users of first-generation low-potency antipsychotics, 26 as users of first-generation high-potency antipsychotics and 122 as users of second-generation antipsychotics. PE was the cause of death in 33 (6.1%) of these subjects using antipsychotic drugs. However, no subject out of 26 classified as first-generation high-potency antipsychotic drug users was diagnosed with PE. Interestingly, in 52% (17 subjects) of the subjects using antipsychotics, where PE was listed as the cause of death, known risk factors for VTE were noted in the medico-legal dossier (Table 9).

In comparison with non-users of antipsychotics, use of first-generation low-potency antipsychotics and second-generation antipsychotics was significantly associated with PE with adjusted odds ratios of 2.4 (95% CI: 1.5-3.9) and 6.9 (95% CI: 4.0-12.1), respectively.

Table 7. Summary of 7 cases of warfarin-induced cerebral haemorrhages, where a drug interaction might have contributed to an increased bleeding risk and where the events were assessed as possibly avoidable. (Paper III)

Suspected interacting drug (daily dose)	Sex	Age	Indication for warfarin treatment	Duration of warfarin treatment	INR value at onset of bleeding	Other predisposing factors	Classification of interactions *	Outcome
Norfloxacin (200 mg)	F	82	AF	7 years	3.5	Vascular disease	C	Fatal
Naproxen (250 mg OD)	F	77	AF	6 years	3.2	Vascular disease	D	Fatal
Paracetamol (4 g), propoxyphene (150 mg)	F	86	DVT	4 weeks	3.3	None	C	Sequelae
Paracetamol (3 g), propoxyphene (65 mg OD), paracetamol (650 mg OD)	F	80	DVT	6 months	3.1	None	C	Fatal
Paracetamol (1-3 g)	F	77	VTE	10 years	2.9	None	C	Sequelae
Paracetamol (4 g)	M	68	Stroke, DVT	2 months	3.7	Meningeoma	C	Sequelae
Tamoxifen (20 mg)	F	84	DVT	> 1 year	3.7	Diabetes, vascular disease, hypertension	C	Sequelae

*According to the Swedish Drug Compendium (FASS); Class C: The interaction may cause altered drug effects or cause ADRs, but these might be controlled with individual dosing and/or measurements of the drug concentration in plasma. Class D: The interaction might have clinical important consequences with severe ADRs or no drug effect, or the drug effects are difficult to control with individual dosing and the combination should be avoided.

Abbreviations: ADR, adverse drug reaction; AF, atrial fibrillation; DVT, deep vein thrombosis; F, female; INR, international normalised ratio; M, male; OD, on demand; VTE, venous thromboembolism.

Table 8. *Crude and adjusted relative risks (odds ratios) for venous thromboembolism in relation to prescription of antipsychotics. (Paper IV)*

Variable	All cases and controls		Cases and controls with unprovoked VTE	
	Unadjusted relative risk (95% CI)	Adjusted relative risk [§] (95% CI)	Unadjusted relative risk (95% CI)	Adjusted relative risk (95% CI)
Any antipsychotics				
Current users [*]	2.01 (1.73-2.33)	1.98 (1.69-2.33)	1.90 (1.56-2.31)	1.84 (1.51-2.25)
Recent users [†]	1.76 (1.22-2.55)	1.55 (1.03-2.33)	1.50 (0.87-2.59)	1.44 (0.83-2.49)
Former users [‡]	1.56 (1.04-2.35)	1.63 (1.05-2.52)	1.75 (1.06-2.89)	1.72 (1.04-2.85)
First-generation low-potency antipsychotics				
Current users [*]	2.29 (1.69-3.11)	2.18 (1.57-3.05)	2.38 (1.61-3.54)	2.27 (1.52-3.37)
Recent users [†]	1.67 (0.65-4.31)	1.36 (0.48-3.81)	1.33 (0.30-5.79)	1.16 (0.26-5.10)
Former users [‡]	1.13 (0.49-2.63)	1.12 (0.44-2.83)	1.29 (0.46-3.66)	1.26 (0.45-3.60)
First-generation high-potency antipsychotics				
Current users [*]	1.82 (1.49-2.22)	1.77 (1.42-2.20)	1.70 (1.31-2.21)	1.65 (1.27-2.15)
Recent users [†]	2.07 (1.38-3.09)	1.72 (1.09-2.69)	1.42 (0.77-2.60)	1.41 (0.77-2.59)
Former users [‡]	1.89 (1.19-2.98)	1.82 (1.11-2.98)	1.91 (1.05-3.47)	1.84 (1.01-3.36)
Second-generation antipsychotics				
Current users [*]	2.41 (1.87-3.11)	2.53 (1.91-3.34)	2.33 (1.66-3.27)	2.29 (1.63-3.22)
Recent users [†]	3.13 (1.54-6.36)	3.40 (1.63-7.22)	4.98 (1.87-13.26)	4.18 (1.55-11.26)
Former users [‡]	0.87 (0.31-2.42)	1.27 (0.45-3.62)	1.21 (0.43-3.42)	1.17 (0.41-3.31)

*Within 90 days before admission or index date among controls.

†Within 91-180 days before admission or index date among controls.

‡Within 181-365 days before admission or index date among controls.

§Adjusted for current use of statins, low dose acetylsalicylic acid, hormone replacement therapy and vitamin K antagonists and discharge diagnoses of stroke, myocardial infarction, arteriosclerosis, heart failure, diabetes mellitus, cancer, surgery, trauma or fracture and pregnancy.

||Adjusted for current use of statins, low dose acetylsalicylic acid, hormone replacement therapy and vitamin K antagonists and discharge diagnoses of stroke, myocardial infarction, arteriosclerosis, heart failure and diabetes.

Abbreviations: CI, Confidence Interval; VTE, venous thromboembolism.

Table 9. Characteristics of subjects with pulmonary embolism as the cause of death using antipsychotic drugs. (Paper V)

Antipsychotics used	Number of cases	Female sex, n (%)	Median age in years (25th-75th percentile)	Number of cases with other known risk factors for pulmonary embolism
First-generation low-potency antipsychotic users	18	8 (44%)	51 (45-59)	8
Levomepromazine	10	5 (50%)	51 (50-59)	BMI>30 (3), acute myocarditis at autopsy (1), cervical carcinoma (1), thyroid gland and renal carcinoma (1)
Thioridazine	3	2 (67%)	50 (50-57)	-
Chlorpromazine	3	-	51 (41-52)	-
Dixyrazine	1	1 (100%)	48	Gastric banding surgery within 10 days before death (1)
Melperone	1	-	63	BMI>30 (1)
Second-generation antipsychotic users	15	6 (40%)	46 (33-52)	9
Clozapine	6	3 (50%)	36 (31-49)	BMI>30 (3), Factor V Leiden mutation heterozygote (1), acute myocarditis at autopsy (1)
Olanzapine	9	3 (33%)	50 (46-52)	BMI>30 (2), ovarian adenocarcinoma (1), schizophrenia with catatonia and prolonged bedrest (1)
Total	33	14	50 (38-56)	17

Abbreviation: BMI, body mass index.

Discussion

Fatal adverse drug reactions (Paper I)

In Paper I the proportion of FADRs was found to be 3% in a Swedish population of deceased who died in a hospital or outside of a hospital. Assuming that this proportion of fatal suspected ADRs can be generalised to the Swedish population, about 3000 deaths each year may be adverse effects to a drug treatment and FADRs would constitute the seventh most common cause of death in Sweden [127]. To the best of our knowledge no similar studies have been published previously. The proportion of FADRs has been estimated in a population by use of death certificates [23, 128], in hospitalised patients [10-12, 21-24] and in ADRs reported to regulatory agencies [106, 129, 130]. The proportion of FADRs in Paper I was 0.5% based on the information available from death certificates. This is similar to the rates of 0.3% and 0.5% found in two previous studies [23, 128]. In hospitalised patients (admitted because of an ADR or experiencing an ADR while in hospital), suspected FADRs have occurred in 0.05-0.95% of all admissions in previous studies [10-12, 21-24]. The proportion of FADRs in deceased hospitalised patients was found to be 6.4% in Paper I, which is somewhat higher than found in two previous studies 4.6% and 5.0%, respectively [10, 23]. In contrast, the proportion was considerably higher (18%) in one study [26]. However, in that study almost 50% of the included fatalities were suspected to be due to various degrees of inappropriateness in choice of drug, dosage (including intoxications) or route of administration [26]. Moreover, only fatalities in one hospital department of internal medicine was investigated [26] whereas all fatalities in one hospital [23] and a meta-analysis of 39 publications where different hospital departments were included [10] were investigated in the other studies. In general, variation in results may be explained by factors such as the medical departments included, drug use patterns, when patients are admitted to hospital, year of study, region, the information the data was based on and how the information was obtained (death certificates, ADR reports, medical records, discharge registers or if data was prospectively collected).

The main strengths of this study were that a population based design was used, that the medical records were reviewed and that the suspected FADRs were evaluated by specialists in pharmacovigilance, clinical pharmacology and forensic pathology. A conservative approach

was used, and only subjects where all the assessors agreed there could be a possible association between the medication used and the suspected FADR were included. The results of this study may still be an overestimation since suspected ADRs were considered. Thus, it is still possible that the effects observed were not related to the drug treatment. Moreover, the deceased subjects were old and frail and although all suspected ADRs were considered to have contributed to the fatal outcome the suspected ADRs might have been of minor importance. The proportion of FADRs may also have been underestimated. Cases might have been missed due to inadequate cause of death diagnosing (only 13% underwent autopsy). In a previous study, an autopsy finding and/or drug analysis were decisive for recognising a suspected FADR in 56% of cases, and in 10% of the remaining patients, similar data was needed to exclude the suspicion of a FADR [24]. Cases might also have been missed due to an inadequate recording in medical case records (*e.g.*, information on use of over the counter (OTC) drugs and herbal remedies may not have been documented).

Haemorrhage was the most commonly observed FADR in Paper I and haemorrhage is also the most commonly reported FADR to the MPA [106]. Antithrombotic agents (16 cases) and platelet aggregation inhibitors (21 cases) were the drug groups most commonly implicated in subjects with FADRs. The drugs and diagnoses implicated in FADRs vary between studies, but haemorrhage in association with anticoagulants is common [22, 23]. All of the observed FADRs in this paper were listed in the Swedish Drug Compendium (FASS) which was expected since the study was not designed to find signals of new suspected FADRs. To detect new suspected FADRs other methods such as spontaneous reporting systems are more useful [131].

Rommers *et al.* [132] have compiled an overview of methods available to reduce ADRs in hospital. They conclude that the risks of ADRs might be reduced by access to unbiased drug information. When a pharmacist was available at an intensive care unit and participated in rounds on the unit for six months, ADRs decreased by 66% [132]. A computerised decision support system may also decrease the number of ADRs, however alerts and warnings might be ignored if irrelevant alerts occur too often.

Fatal intoxications (Papers I, II)

In Paper I and Paper II antidepressants, analgesics and sedatives were commonly associated with fatal intoxications in Sweden. Substances used in subjects with an intoxication usually reflects the toxicity but also the sales and use of that substance [34, 133]. In Paper II propoxyphene was the most commonly detected pharmaceutical substance. In a large proportion (>70%) of the subjects where this substance was found it was detected in concentrations above the cut-off value. The number of cases where propoxyphene was detected has decreased since 1997. This is probably due to the studies published on the toxicity of propoxyphene during 1998-2002 [133-136], that was followed by regulatory actions in 2001 and in 2005. In 2001 a special prescription form was initiated for propoxyphene and in 2005 combination preparations containing paracetamol and propoxyphene were withdrawn from the market. A simultaneous rise in the number of deaths attributed to tramadol was observed. Tramadol is an opioid analgesic used to treat moderate to

severe pain (similar to propoxyphene). Compared to propoxyphene, tramadol produces little respiratory depression [43] and the risk for unintentional intoxication due to tramadol is lower [43, 137, 138].

In individual cases it is difficult to conclusively establish the contribution of an individual drug to the fatal outcome. Even in living patients, interpretation of a single blood concentration measurement is difficult if there is, for example, no information on route of administration, time of intake or number of doses taken [139]. Moreover, due to *postmortem* metabolism [111] and *postmortem* redistribution of substances [140], the drug levels may vary between sampling site and the interval between death and when the specimen is collected. Only substances detected in femoral blood were used in Paper II since it appears to be the specimen least subject to *postmortem* redistribution [140]. Since more than one substance usually is ingested in subjects with a fatal intoxication [25, 27, 28, 30] the effects of the separate drugs used may be reinforced by a known or unknown drug-drug interaction. Moreover, paracetamol, for example, has a delayed toxicity [141] and concentrations of paracetamol at time of death may not be elevated. A number of different methods have been described in the literature to overcome these problems when making compilations of drugs used in fatal intoxications. The principal drug responsible for the intoxication may be assessed by taking the ratio between the measured concentration of a substance and the therapeutic concentration of that substance [142]. Schreinzer *et al.* [143] used a relative intoxication index (also called fatal toxicity index or fatality ratio [144, 145]) where the number of intoxications involving a certain drug was related to sales of that drug. Other studies have not assigned a principal drug responsible for the intoxication [42, 146, 147]. Instead the influence of different drugs in ethanol intoxications was measured by analysing concentrations of ethanol when present alone or in combination with certain drugs.

In Paper II cut-off values were used. In subjects where the substance was detected above the cut-off value, the substance was considered to have contributed to the fatal outcome. The cut-off values are approximate and the proportion of subjects with high concentrations with a certain substance should be interpreted with caution. In Paper II, the cut-off values were based on a Swedish compilation of fatal and non-fatal concentrations of drugs in *postmortem* femoral blood [108]. The compilation in Paper II may be used to study changes in the pattern of substances associated with fatal intoxications. It might hence be possible to elucidate new trends in drugs used, introduce preventive measures and to monitor effects of this preventive work. For example in 2005, an increase in the proportion of subjects with high concentrations of hydroxyzine was observed, compared with the period 1992-2002 (61% vs. 34%). This increase was discussed with the MPA and the Poison Information Centre. However, no actions were taken since the actual number of cases involved was small.

Warfarin-related cerebral haemorrhage (Paper III)

As observed in Paper I, warfarin is one of the substances most commonly implicated in fatal suspected ADRs. In Paper III 10% of the identified patients with haemorrhage were treated with warfarin and the fatality rate was high (44%). Whether ADRs can be avoided is a critical question. Haemorrhage associated with warfarin treatment could be categorised as type A ADRs and the risk of haemorrhage may be reduced by careful monitoring of the therapeutic effect [15].

In this study 12% of the cerebral haemorrhages were considered to be caused by warfarin-drug interactions that were possibly avoidable. Assessing avoidability is however a rather complicated matter. Based on the information available in each case, the cerebral haemorrhage was considered possible to avoid in patients where naproxen, norfloxacin, paracetamol, propoxyphene or tamoxifen concomitantly were used with warfarin. Increased effects of warfarin have been observed in patients treated with warfarin and norfloxacin [148, 149], even a case of fatal ICH [150]. In contrast, after a single dose of warfarin no pharmacokinetic or pharmacodynamic changes were observed in 10 healthy subjects treated with norfloxacin for six days [151]. NSAIDs inhibit the synthesis of prostaglandines, and therefore inhibit platelet aggregation [152]. No significant pharmacokinetic interactions have however been associated with concurrent treatment of naproxen and warfarin [152, 153]. Moreover, two case-control studies did not find an association between use of NSAIDs alone and ICH [154, 155]. The anticoagulant effect of warfarin is normally only slightly affected by small occasional doses of paracetamol [156]. However, larger doses of paracetamol taken regularly for longer periods of time might affect the warfarin metabolism [157-159]. When lower doses of paracetamol are used in combination with propoxyphene, an increase of the prothrombin time has been reported [160]. The anticoagulant effect is markedly affected when warfarin is combined with tamoxifen [161-163].

When starting treatment with warfarin, full anticoagulation is not achieved until several days after treatment initiation due to the long half-lives of some of the coagulation factors [63]. Therefore, heparin, an anticoagulant that acts upon antithrombin, is co-administered during the initial treatment with warfarin. Interactions between these anticoagulants were hence considered not avoidable. Moreover, the potential interaction between warfarin and acetylsalicylic acid was considered not avoidable since there is evidence that there is only an increased risk for ICH when used in moderate to high doses (>1225 mg/week) [164].

Interactions with selective serotonin reuptake inhibitors (SSRIs) and dipyridamole were considered inevaluable. Only mild bleedings have been observed in patients treated with dipyridamole and SSRIs [165-168] and there is conflicting evidence whether these drugs have clinically significant interactions with warfarin. SSRIs may impair platelet aggregation by depleting serotonin levels in platelets directly and increasing the risk for haemorrhage. A significant increase in prothrombin time has been observed for citalopram [165]. Some SSRIs, particularly fluvoxamine and fluoxetine may also inhibit the oxidative metabolism of the S-enantiomer of warfarin via CYP2C9 [166, 167]. Citalopram and sertraline have low interaction potential with warfarin [165, 169]. Although bleedings have been observed in

users of SSRIs, no increased risk for ICH has been observed [168].

The main strength of this study is that we were able to review the medical records of patients with a diagnosis of intracranial haemorrhage. However, some cases might have been overlooked due to the retrospective design and shortcomings of the medical record coding system (information on OTC drugs, herbal or nutritional products, which might also interact with warfarin are rarely available in medical records). Moreover, it was not possible to assess whether the treating physician had increased the frequency of INR monitoring and/or made warfarin dosage adjustment when concomitant drugs were introduced.

Although the risk of haemorrhage may be reduced by increasing the frequency of monitoring (and, in turn, warfarin dosage adjustment), warfarin-drug interactions do not necessarily result in INR changes (pharmacodynamic interactions). In general, antiplatelet drugs (*e.g.* acetylsalicylic acid) and all NSAIDs should be avoided in combination with warfarin [81]. Warfarin treatment should be evaluated whenever concomitant drugs are introduced, stopped or if any of the other risk factor for haemorrhage change [64]. Involving the patient actively in the treatment seems crucial to improve safety of warfarin treatment. Today it is possible for patients to manage their own anticoagulation therapy [170]. Patients test their own INR value, the results are discussed with the treating physician who adjusts the dosing of warfarin (self-monitoring) or the patients adjust the dosage of warfarin on their own (self-management). The risk of VTE and haemorrhage has been shown to be reduced using both strategies [171]. The major advantage of these systems is that dosage adjustments are not delayed. However, an inaccurate value may be obtained if the test is not performed correctly and the regimen is not suitable for all patients [170, 171].

Antipsychotics and risk of venous thromboembolism (Papers IV, V)

In Paper IV we observed a 2-fold increased risk of VTE in patients currently being prescribed antipsychotics compared with non-users. The risk of VTE was higher in users of second-generation antipsychotic drugs compared with users of first-generation high-potency antipsychotic drugs. No difference in risk of VTE was observed between users of first-generation low-potency antipsychotics and users of first-generation high-potency antipsychotics or second-generation antipsychotics. Moreover, we found an increased risk of VTE in former users of any antipsychotic drugs, the confidence interval was however wide and no solid conclusion could be drawn based on this finding. In Paper V we observed a 2-fold and 6-fold overrepresentation of fatal PE in users of first-generation low-potency and second-generation antipsychotic drugs, respectively, in a medico-legal autopsy series. No solid conclusion regarding the risk of fatal PE in users of first-generation high-potency antipsychotics could be drawn since several of these substances were not included in the routine *postmortem* analyses and therefore only detected in few subjects. Previous studies have found a two- to 11-fold increased risk of VTE [93-96, 99, 100] in users of antipsychotic drugs. None of the previous studies have been able to observe an increased risk in users of both first-generation antipsychotic drugs and second-generation antipsychotic drugs [94, 95]. Moreover, only two studies [94, 95] have looked at the risks of VTE in current and recent users of antipsychotic drugs, but not in former users. No increased risk of VTE was observed

in recent users of antipsychotic drugs. Only Walker et al. [93] have compared the risk of VTE in current users compared with former users of clozapine, and they found a 5-fold increased risk of fatal PE in current users of clozapine. The results of Paper IV and Paper V in combination with previous studies suggest that users of antipsychotic drugs have an increased risk of VTE. Since there might be an increased risk of VTE in former users of antipsychotic drugs as well, further studies are warranted to elucidate whether the increased risk is due to use of antipsychotic drugs or the underlying disease.

The main strength of Paper IV and Paper V is that data on outcome and exposure was recorded prospectively. The population based design in Paper IV is also a major strength. Age is an important risk factor for VTE [103], which was controlled for in both studies and in Paper IV other important risk factors for VTE were also controlled for. Although confounding factors were controlled for in both papers, unmeasured confounding might be present and the results may have been biased. In Paper IV there was no information on compliance available or duration of actual drug use. In Paper V we know that antipsychotic drugs were used since the drugs were detected *postmortem*. There was however no information available with regards to the duration of drug use.

Several factors have been proposed as mechanisms explaining the increased risk of VTE observed in antipsychotic drug users [112]. All situations associated with immobilisation increase the risk of VTE [103], *e.g.* bedrest is associated with a 9-fold increased risk. Psychotic patients might be immobilised due to sedation, a common adverse effect of many antipsychotic drugs [112] especially first-generation low-potency antipsychotics [172] and clozapine [173], or patients diagnosed with severe psychotic conditions may in fact require immobilisation through sedation or mechanical restraint. Another risk factor for VTE associated with patients with schizophrenia, with or without treatment with antipsychotic drugs, is obesity. Clinically significant weight gain is four times more common among patients with schizophrenia than in the general population [91]. Moreover, treatment with clozapine and olanzapine are the antipsychotic drugs associated with most weight gain [91, 174], where 12-36% of patients using clozapine have been observed to gain weight [91]. Weight gain is associated with a 1.0-4.5-fold increased risk of VTE [103, 175, 176]. However, in previous studies investigating the association of VTE and use of antipsychotic drugs [94-96, 98, 100] where body mass index (BMI) has been controlled for, the increased risk of VTE remained after adjustment in a multivariate model. Moreover, more psychiatric patients smoke [90, 177-179] compared with the general population (58-68% vs. 25-42%) and patients with schizophrenia smoke more cigarettes per day. Whether smoking is associated with VTE is under discussion [104, 116, 175, 180], but smoking is not considered a major risk factor for VTE. Chronic obstructive pulmonary disease (COPD) has however been proposed to increase the risk for VTE [104, 181-183]. Moderate homocysteinaemia (15-100 μM) has been associated with a 2-3-fold increased risk of VTE [103, 184] and homocysteine levels of 5.9-74.8 μM have been observed in patients with schizophrenia [185-189]. Antipsychotic drug treatment has also been associated with an enhancement of platelet aggregation [89, 112, 190-194]. In patients treated with antipsychotic drugs, elevated levels of prolactin correlated with activation of platelets have been observed [192]. Moreover, clozapine has been

associated with platelet adhesion and aggregation *in vitro* [190]. Raised levels of antiphospholipid antibodies including lupus anticoagulantia and anticardiolipin antibodies have been observed in patients treated with antipsychotic drugs [112, 195-198], which has been associated with a relative risk of VTE of 3.6 [103].

Some of the factors, proposed as mechanisms explaining the increased risk of VTE in antipsychotic drug users, may be prevented, if recognised. The first step to reduce VTE in patients treated with antipsychotic drugs is hence to monitor the physical health of these patients [92, 199]. Meltzer *et al.* [200] have suggested an algorithm assessing cardiac and metabolic risks in these patients. One of the major risk factors for VTE is obesity. Methods to prevent excessive weight gain like strict diets, if possibly switching from olanzapine and clozapine to an antipsychotic drug less associated with weight gain, or to add drugs to treat the obesity, is suggested as measures to decrease the risk of VTE in these patients [91, 174]. Moreover, homocysteine levels might be lowered with intake of vitamins, *e.g.* folic acid, B-12 and pyridoxine [201]. In patients with longer periods of immobilisation prophylactic treatment could be considered [112].

The use of different data sources in pharmacovigilance

A spontaneous reporting system is considered to be an important method for surveillance of drug safety as a means to detect new safety signals after marketing [131]. The utmost advantage with spontaneous reporting schemes is that all drugs during their entire life span among all users are included. In Paper I and Paper III, one (2%) and two (3%) of the suspected ADRs were reported to the MPA, respectively. Underreporting of suspected ADRs is a well-known disadvantage with spontaneous reporting systems. Previously less than 15% of all serious and 2-4% of non-serious ADRs have been reported [14, 131, 202, 203]. Higher reporting rates have been found, for example 36% of the subjects using combined oral contraceptives experiencing a fatal VTE were reported to the regulatory agency in one study [204]. The rate of reporting is affected by several factors such as the length of time the product has been on the market [131, 202]. Moreover, ADRs are more likely to be reported if the ADR is serious, unrecognised or related to a new drug [202].

In Paper IV the Danish prescription registers were used to obtain information on drug use in a population of cases with a VTE diagnosis and in controls without a VTE diagnosis. The main strength with using prescription register data is that the entire population is covered. However, only reimbursed drugs are included (sedatives, hypnotics, oral contraceptives, laxatives and certain other drugs). Hence, use of oral contraceptives (an important risk factor of VTE) could not be controlled for in the analyses in Paper IV.

In Paper III data was extracted from hospital discharge registers in Östergötland to identify patients with a cerebral haemorrhage. In Paper IV data was extracted from Danish discharge registers for patients with a diagnosed VTE and control subjects. The main strength of these registers is that data is easy to extract on a predefined set of patients. However, errors in coding might limit the usefulness of discharge registers. The quality of the diagnosis coding in Sweden has been evaluated in 1986 and 1990. In total 17% of the discharge diagnoses

reported were wrong, often due to transcription error, coding errors and incorrect diagnoses [113]. The information in the Danish discharge registers has been evaluated as well. In North Jutland County [205], the VTE diagnoses were not confirmed in the medical records in 13% of cases. However, if errors in coding are unrelated to exposure, the risk for VTE is likely to be underestimated [53, 56, 60, 205]. Hence, patients might have been missed in Paper III and patients might have been misclassified in Paper IV.

An important source for studies on fatalities is the Cause of Death Register where all fatalities in Sweden are registered. There is however no information on drug use available and suspected ADRs are rarely reported. In Paper I 16% of the suspected FADRs were noted on the death certificates whereas all but one of the fatal intoxications were recorded. In a US study [206], fatal intoxications were the most common drug-related deaths based on the information in death certificates. Hence the information in a cause of death register may be a valuable means to identify certain cases, but further data is needed to evaluate suspected ADRs.

The main strength with the information in the forensic pathology and forensic toxicology databases is that an autopsy has been performed and the drugs stated to be used by the subject actually were found *postmortem*. Data is also likely to be entered correctly in the databases since the information entered is checked several times because the databases constitute real-time database systems integrated with the routine cases management systems at all forensic units in Sweden and the data entered has to be verified by the forensic pathologist and the forensic toxicologist [101]. The main limitation when using the forensic databases when studying suspected FADRs is that the population subjected to a forensic autopsy are selected and may differ from other deceased subjects. The criteria for when a medico-legal autopsy should be requested by the police are, although defined in national regulations, not always applied in a similar way by different police authorities. Even though the *postmortem* routine analysis covers more than 200 substances, some drugs (*e.g.* illicit drugs and antipsychotics) are analysed only when an intake is suspected. Accordingly, users of certain antipsychotic drugs might hence have been missed in Paper V. Additionally, there is incomplete information in the databases as regards to use of other drugs not included in the screening but with possible effects on the coagulation system (*e.g.* use of oral contraceptives and HRT), other diseases not contributing to death and other factors such as BMI and smoking habits. Most subjects with suspected fatal intoxications are subjected to a forensic autopsy and in 7 (78%) of the 9 subjects with a suspected drug intoxication in Paper I were subjected to a medico-legal autopsy. The forensic pathology and forensic toxicology databases may be useful when studying new signals of sudden FADRs and to study changes in the pattern of substances used in fatal intoxications. Although it should be noted that the rate of fatalities subjected to forensic autopsies might differ between regions in Sweden and the results might not be representative for all regions.

It is important to continue to employ the use of different registers, such as those presented in this thesis, as they are important tools in the evaluation of new suspected ADRs and FADRs. It would be of great interest to continue to explore the possibilities and limitations of all these

databases in the elucidation of suspected ADRs. However, to be able to study rare exposures and rare events a large source population is needed. Since similar medico-legal databases and health care databases exist in the other Nordic countries [44, 115, 207-210] it might be useful to initiate collaborations with our neighbours when investigating new suspected ADRs and FADRs.

Conclusions

My findings suggest that FADRs contribute to a significant health care burden and substantial number of deaths. Haemorrhage is present in a majority of the FADRs and antithrombotic agents or NSAIDs are implicated in most of these events. Preventive measures should be taken to reduce the number of drug-related morbidity and mortality events.

Drug-related fatal intoxications seem to be relatively common. Therefore it is necessary to observe changes in patterns of substances associated with fatal intoxication to be able to discover new trends and to be able to monitor effects of preventive work. There is always a risk that when a drug becomes less available or less desirable due to restrictions and information, a new drug with a less documented safety profile will take its place.

Warfarin-induced cerebral haemorrhage is a major clinical problem with a high fatality rate. A significant proportion of such reactions are caused by drug-drug interactions that are considered possible to avoid. To decrease the risk for haemorrhage in patients treated with warfarin caution should be taken when using drugs known to interact with warfarin and the warfarin effect should be monitored more intensively.

Users of antipsychotics may have an increased risk of VTE and an increased risk of fatal PE. Whether the increased risk is due to the use of antipsychotic drugs or the underlying disease requires further investigation. Studies are also warranted to identify predisposing factors and possible mechanisms.

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