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DRUG-RELATED PROBLEMS WITH SPECIAL EMPHASIS ON DRUG-DRUG INTERACTIONS

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Painter of the elderly lady on the front cover: Rebecca Edwards

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To my family

ABSTRACT

The aim of this thesis was to address some aspects of drug related problems with special regard to drug-drug interactions.

In ***paper 1*** we aimed to describe the scenario and frequency of drug-related problems (DRPs) in in-patients and to determine whether a pharmacotherapeutic advisory intervention aiming at reducing DRPs could affect rates of re-hospitalisation and / or death within 6 months. A total of 299 DRPs among 71% (106/150) of the patients were found, who had not previously been identified in the usual care. Thirty-five per cent (106/299) of DRPs in 39% (58/150) of the patients were judged to be of such importance that advice was given to the physician in charge. The proportion of re-hospitalisation and death in the intervention group was 49% (73/150) compared to 46% (69/150) in the control group (Risk ratio: 1.06, 95% confidence interval: 0.84 to 1.32, P=0.64). In conclusion, drug-related problems were common. The impact of drug-related problems on hard endpoints such as re-hospitalisation and death may however be overestimated. It is of importance to clarify if and in what way drug-related problems are preventable.

The purpose in ***paper II*** was to evaluate the clinical relevance of the Janus Web application in screening for potential drug-drug interactions. One hundred and fifty DDIs, regarding 58 different interaction pairs, were classified as significant. 126 interactions that were significant by definition did not result in advice. A look at the alerts which featured most frequently in such combinations illustrates the nature of this discrepancy. With the aim to develope a drug-drug interaction software with the goal of achieving and maintaining a general use on a routine basis, it is of great importance that the alerts are clinically relevant. Equally important may be to present the warnings in an adequate way to give the prescribing physician a balanced picture of the problem and thereby avoid “alert fatigue”.

In ***paper III*** we evaluated if steady-state plasma levels of risperidone or the corresponding active moiety differed between patients exposed to 1 or several drugs defined as either substrates or inhibitors of the hepatic cytochrome P450 enzyme 2D6 (CYP2D6). The median concentration-to-dose (C/D) ratio of risperidone in patients with 0, 1 or >1 was 2.6, 8.5, and 17 nmol/L/mg, respectively ($p<0.001$). All of the medication lists in the 7 patients with >1 inhibitor of CYP2D6, included fluoxetine, paroxetine, thioridazine and/or levomepromazine, i.e. drugs known as potent inhibitors of CYP2D6. The “active moiety” (risperidone + 9-OH-risperidone), in patients with different numbers of concomitant CYP2D6 inhibitors was 17, 24 and 30 nmol/L/mg, respectively ($p<0.01$). We concluded that an increase in the number of concomitant inhibitors may be associated with a lower CYP2D6 activity, although the type of inhibitor is probably more important. Drug-dependent inhibition of CYP2D6 increases the “active moiety” of risperidone. An indication for risperidone TDM should consequently include concomitant medication with established CYP inhibitors.

In ***paper IV*** we used the Swedish prescribed drug register to determine whether doctors are taking potential drug-drug interactions (DDIs) for serotonin reuptake inhibitors into account in the prescribing decision. The use of *CYP2D6-drugs* (metoprolol, donepezil, galantamine, codeine, tamoxifen) together with CYP2D6-blocking SSRI (paroxetine, fluoxetine) or SSRI that do not block CYP2D6 (citalopram, escitalopram, sertraline) was analysed, and related to

the use of CYP2D6-independent *comparator drugs* (atenolol, rivastigmine, propoxyphene, anastrozole). Compared with patients who where dispensed citalopram/sertraline, patients dispensed fluoxetine/paroxetine faced a reduced risk of receiving metoprolol (adjusted odds ratio, 0.80; 95% CI, 0.76 to 0.85), donepezil (0.65; 0.49 to 0.86) and galantamine (0.58; 0.41 to 0.81). In contrast, the risk of receiving the prodrugs codeine (instead of propoxyphene) or tamoxifen (instead of anastrozole) was similar among patients on fluoxetine/paroxetine compared to citalopram /sertraline (adjusted odds ratios, 1.03; 95% CI, 0.94 to 1.12 and 1.29; 95% CI, 0.96 to 1.73 respectively). The results, suggest that drug-drug interactions (DDI) related to reduced bioactivation of pro-drugs may be more easily neglected in clinical practice, as compared to DDI that cause overt adverse drug reactions.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following papers, referred to in the text by their Roman numerals:

I. **Mannheimer B**, Ulfvarson J, Eklof S, Bergqvist M, Andersen-Karlsson E, Pettersson H Bahr CV.
Drug-related problems and pharmacotherapeutic advisory intervention at a medicine clinic.
Eur J Clin Pharmacol 2006;62(12):1075-81.

II. **Mannheimer B**, Ulfvarson J, Eklof S, Bergqvist M, von Bahr C.
A clinical evaluation of the Janus Web Application, a software screening tool for drug-drug interactions.
Eur J Clin Pharmacol 2008;64(12):1209-14.

III. **Mannheimer B**, Bahr CV, Pettersson H, Eliasson E. Impact of Multiple Inhibitors or Substrates of Cytochrome P450 2D6 on Plasma Risperidone Levels in Patients on Polypharmacy. *Ther Drug Monit* 2008;30(5):565-69.

IV. **Mannheimer B**, Wettermark B, Lundberg M, Pettersson H, Bahr CV, Eliasson E. Important differences in adherence to drug label recommendations on metabolic interactions between commonly used drugs - a nationwide cross-sectional register study.
Submitted

CONTENTS

LIST OF ABBREVIATIONS

ADR	Adverse drug reactions
CDSS	Computerised decision support systems
CPOE	Computerised physican order entry
CYP	Cytochrome P450
CYP2D6	Cytochrome P450 enzyme 2D6
DRP	Drug-related problems
DDI	Drug-drug interaction
DDD	Defined daily dose
HIT	Health information technology
JWA	Janus web application
NSAID	Non steroid anti inflammatory drug
PCNE	Pharmaceutical care network Europe
SFINX	the Swedish Finnish drug interaction X-referencing
SSRI	Selective serotonine reuptake inhibitors
TDM	Therapeutic drug monitoring

1. BACKGROUND

1.1 Introduction

Primum, non nocere – above all, do no harm. This motto, attributed to Hippocrates has guided medical practice for over 25 centuries and has been brought to date by the last decade's growing body of evidence concerning harm due to drug treatment.

Improvements in health care have during the last century contributed to a substantial decrease in mortality and morbidity. Life expectancy due to clinical preventive and curative services has been estimated to have increased 5 years in industrial countries. The discovery of insulin, sulphonamide, penicillin, the initiation of immunisation programs for children and improvements in the treatment of ischemic heart disease, are considered most important in this regard.[1]

However, with the recent rapid development of potent drugs, prescribed to large groups of patients, concerns regarding their harmful effect have been raised. The epidemiological finding that over 100 000 deaths occur in the United States annually due to Adverse Drug Reactions (ADR),[2] supported by a growing number of reports from other Western world countries, has brought the subject to the top of the policy agenda and the forefront of public debate world wide.

1.2 Clinical consequences of Drug-Related Problems -The epidemiology of Adverse Drug Reactions

Drug-Related Problems **(**DRP) is a concept designed to be used in medication reviews. The term is wider as compared to ADRs as it also covers problems that may interfere with desired health outcomes but has not (yet) done so. Examples include a drug combination that may, result in an ADR, or a dose being too high or too low.[3] In this section I will however focus mainly on the narrower term ADRs due to the by far more available data, which enables more distinct conclusions regarding its impact on the general health.

The estimations of the occurrence of ADRs vary largely due to differences in health care settings, to the use of different definitions on which these estimations are based and to interindividual differences in how the same definitions are applied. The proportion of admission rates to in-patient clinics associated with ADRs thus ranges from 0.2-21.7%.[4 5] Pirmohamed et al. who performed the up to this date largest prospective analysis of admissions to hospital, that included 18 820 patients, estimated that 6.5% of these were due to ADRs. [5] At inpatient clinics, the incidence of ADRs ranges between 0.6 and 14.7%.[6-9]

The overall fatality due to ADRs was estimated to 0.15% by Pirmohamed et al., based on the outcome of the total number of admissions. Deaths due to gastrointestinal bleedings were the most common.[5] Lazarou et al. estimated the corresponding figure to 0.32% focusing on in-patients. Extrapolating this number to all of the United States suggest that 106 000 people die annually due to ADRs which would make these reactions the fourth leading cause of death after heart disease, cancer and stroke.[2] A

recently published Swedish population based study estimated fatal adverse drug reactions to account for approximately 3% of all deaths which would make it the 7th most important.[10]

To estimate the cost attributable to adverse drug reactions may be somewhat speculative, but a prospective cohort study suggested a total cost of $5.6 million dollars for a 700-bed teaching hospital. Extrapolating these figures to the whole American population, it was estimated that for every dollar spent on drugs another dollar is spent on treating the consequences of adverse drug events.[11] A review including 108 studies involving 412 000 patients in Europe estimated the overall ADR impact to 4 out of 100 hospital beds which would result in an annual cost of 380 million pounds only in England.[12]
Although the consequences of DRPs and ADRs may be difficult to overview due to the use of different designs across various health care settings and countries all over the world, they do indeed indicate a large problem in today's health care.

1.3 Terminology

Table 1 lists some terms related to drug related problems and their definitions. The Pharmaceutical Care Network Europe (PCNE) has constructed a scheme, used to classify drug related problems that has been validated.[3] It is structured in a hierarchal manner with separate codes for problems, causes and interventions, and hereby fulfils the criteria identified to be crucial for successful medication reviews.[13] The WHO definition of an ADR that has been in use for nearly 40 years is "one that is noxious, is unintended and occurs at doses normally used in man".[14] ADRs are often categorised into type A and type B respectively. They are for mnemonic purposes labelled "Augmented" or "Bizarre". Type A ADRs are thus common and related to dose and to the pharmacological action of the drug. They are therefore often predictable. Type B reactions are on the other hand uncommon, not related to the pharmacologic action of the drug and unpredictable or idiosyncratic.[15] The diagnosis of an ADR for example in a study aiming to determine their occurrence in a particular setting usually involves assigning a probability of the causation and sometimes an estimation of whether it could have been avoided. The causality is hereby categorised from unlikely to certain based on the relation between the use of the drug and the occurrence of the reaction and the possibility to distinguish the symptom from such emanating from underlying diseases independent from co-dispensed drugs.[19] The avoidability is based on whether the event was due to a drug treatment procedure consistent with present day knowledge of good medical practice or not.[17]

Table 1. Some important definitions related to drug-related problems

Drug Related Problem[3]	A Drug-Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.
ADR[18]	An adverse reaction to a drug is one that is noxious, is unintended and occurs at doses normally used in man
Cause effect relationship for ADRs[19]	
Definite	A reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissues; that follows a known response pattern to the suspected drug; and that is confirmed by improvement in stopping the drug (dechallange), and reappearance of the reaction on repeated exposure (rechallange).
Probable	A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known response pattern to the suspected drug; that is confirmed by dechallange; and could not be reasonable explained by the known characteristics of the patient's clinical state
Possible	A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known response pattern to the suspected drug; that is confirmed by dechallange; and could not be reasonable explained by the known characteristics of the patient's clinical state
*Conditional**	A reaction that follows a reasonable temporal sequence from administration of the drug that does not follow a known response pattern to the suspected drug; that does not follow a known response pattern to the suspected drug; but that could not be reasonably explained by the known characteristics of the patient's clinical state.
Doubtful	Any reaction that does not meet the above criteria.
Avoidability assessment for ADRs[17]	
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.
Possible 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.
Type A reactions[15]	ADRs that are common, related to the pharmacological action of the drug, often predictable (Augmented) and associated with low mortality. Examples include digoxin toxicity and anticholinergic effects of tricyclic antidepressants
Type B reactions[15]	ADRs that are uncommon, not related to a pharmacological action of the drug and therefore unpredictable (Bizarre) and associated with high mortality. Examples include penicillin hypersensitivity and idiosyncratic reactions such as malignant hyperthermia.

*The function of this category is to retain temporarily those cases that may be manifesting a yet undescribed ADR, and to allow later reclassification of the case when more information becomes available.

1.4 Different ways to address Drug Related Problems

The pursuit to decrease the clinical consequences of Drug Related Problems (DRPs) can be categorised into two broad categories:

1) to identify the risks of ADRs
2) to ascertain that this knowledge is applied in clinical practice

Most ADRs fall into the type A category as they can be predicted from the drug dose put in relation to knowledge regarding physiological and environmental factors such as age, kidney function, and co-dispensed drugs. It is therefore important to study the relation between these factors and the risk for ADRs. This can be done for example by studying the relation between these factors and the plasma concentration of a particular drug or to the prevalence of ADRs for example in a Therapeutic Drug Monitoring (TDM) setting (see below).
The use of an epidemiologic strategy and registers such as the Swedish prescribed drug register (see below), for example to look at dispensing patterns and their association with a clinical outcome, usually enables the researcher to include larger patient samples sometimes at the cost of diminished quality of collected data.
The monitoring and analysis of spontaneous reports of ADRs in pharmacovigilance units is important in detecting new ADRs or determining the incidence of ones already detected.

Equally important is to apply the knowledge regarding ADRs to clinical practice. Central policies based on available evidence are produced by international or national organs and modified to comply with local legislations and health care traditions at sub national level. Expert resources used to support the routine care are sometimes supplied such as locally employed pharmacists or clinical pharmacologists whose action may be evaluated in studies. Apart from personal resources, health care information technology such as Computerised Physican Order Entry (CPOE) and Computerised Decision Support Systems (CDSS) has a large potential to prevent drug related problems (see below).

1.4.1 Drug treatment in the elderly

When aiming at preventing ADRs it is of importance to address groups that are at particular risk for problems due to the treatment of drugs. One especially vulnerable group are the elderly.[20] The reasons for this include an increased exposure for drugs, in terms of number of co-dispensed drugs used in combination as well as the level of plasma concentration per given dose in combination with an increased sensitivity for drugs.

Elderly individuals are indeed dispensed a large number of drugs, and the numbers have increased. Nursing home residents as well as elderly people living at home with multi morbidity are dispensed in average 10 drugs concurrently.[21-23] A longitudinal Swedish study showed that concurrent medication in individuals in a general population 81 years or older increased from 3.4 drugs during 1987-1989 to 4.6 drugs during 1994-1996.[24]

Physiological changes in the elderly resulting in alterations in drug exposure regards all four major pharmacokinetic entities; absorption, distribution, metabolism and excretion.[25] Most important are however changes in elimination due to a decreased kidney function. Between the age of 40 – 70, the kidneys ability to filter blood is decreased by 30 – 40 %.[26 27] The elimination of water soluble drugs such as diuretics, digoxin and some antibiotics are hereby decreased. Serum creatinine is commonly used to estimate renal function. Mean serum creatinine values, however, fail to increase with age because creatinine production, which is dependent on muscle mass, falls at nearly the same rate as the renal clearance of creatinine.[28] Renal impairment is thereby masked in the elderly. Fortunately simple algorithms have been developed that estimate renal clearance without having to collect urine. Cockroft and Gault thus developed a formula to predict creatinine clearance from creatinine age and body weight.[29] It is still widely used and accessible in the web based version of the Swedish Physicians' Desk Reference (FASS) in a modified version.[30]

Pharmacokinetic alterations, associated with old age are accompanied by a progressive decline in counter regulatory (homeostatic) mechanisms. Therefore, many physiologic responses are usually stronger than in the younger population, which increases the risk of ADRs. Examples include postural hypotension with agents that lower blood pressure and hypoglycemia with antidiabetics. The brain is an especially sensitive drug target in old ages. One important reason is the accompanying decrease in the number of dopamine D2-receptors which contributes to a sensitisation of drugs that block dopaminergic action such as neuroleptics.[25 31] For these reasons the elderly are of special interest when applying any part of the research strategies discussed below.

1.4.2 Inter - individual differences in drug exposure

Although most ADRs (type A reactions) are claimed to be dose related, predicting ADRs based on no other information than the dose would be difficult. The reason for this is that human beings differ in absorption and elimination and the same dose therefore results in large differences in drug concentration at the site of action. Differences in drug concentration between two individuals with the same weight on the same dosage can vary greatly.[32] In fact, the daily dose corrected plasma concentrations of risperidone in 218 patients did, according to our own data, range from 0.45 - 58 nmol/L/mg (Figure 1). Other commonly used drugs with a large interindividual variability in dose-plasma concentration relationship, often associated with adverse drug reactions include amitriptyline, olanzapine and warfarin.[33-35] This variation can be of genetic, physiological, patophysiological or environmental origin.

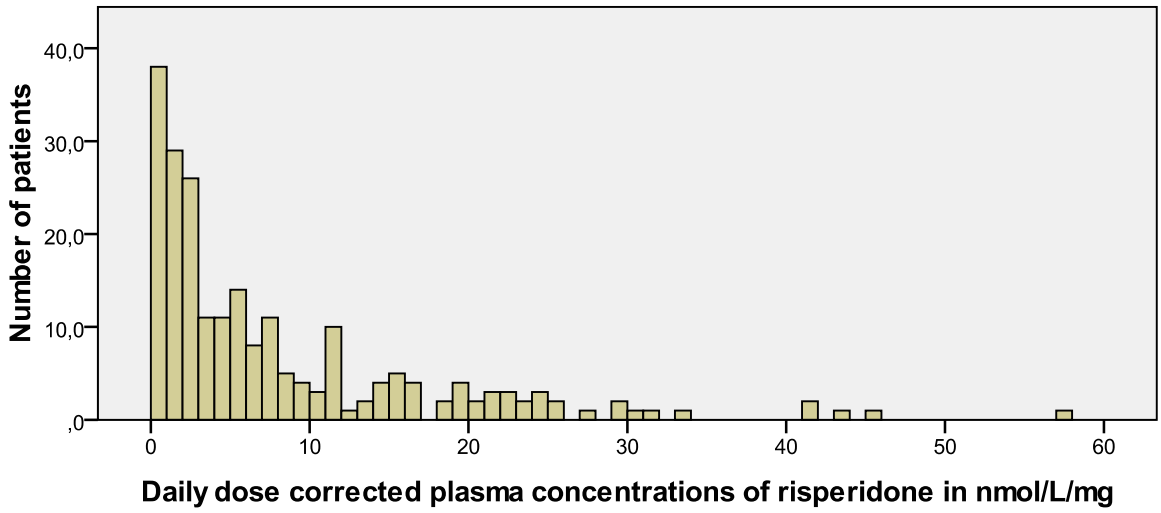
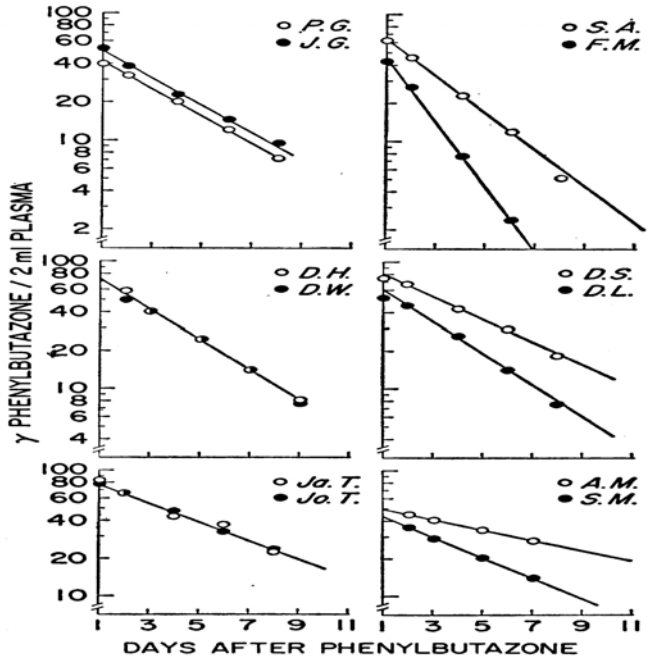


Figure 1. *Variability in exposure to risperidone in 218 individuals*

1.4.2.1 Pharmacogenetics

In 1967, Hammer and Sjöqvist showed that the steady state plasma levels of desmethylimipramine and nortriptyline were bimodally distributed, which indicated that pharmacogenetic factors were important for their metabolism.[36] Some by now classic studies published 1968 by Vessel and Page provided further evidence that the elimination of drugs could be mainly genetically controlled instead of environmentally. The first compared the variability of plasma concentrations after the administration of single oral doses of the NSAID phenylbutazone, between monozygotic and dizygotic twins. Half-life between monozygotic twins were thus less variable than between two dizygotics Figure 2.[37] It is now well known that inheritance does constitute an important source of variability regarding response, as well as toxicity following the administration of drugs. Genetic factors are generally estimated to explain 15%-30% of inter-individual differences in drug metabolism but can for some drugs account for up to 95% of the variability.[32]



Copied from Vessel, E and Page J 1968 with permission from The American association for the advancement of science.

Figure 2. *Less variability in the half - life of phenylbutazone in three sets of identical twins (left) compared to three sets of fraternal twins (right).*

1.4.2.2 Environmental differences

There are several environmental factors known to contribute to the observed variability in drug exposure. Cigarette smoke induces several enzymes used for the metabolism of drugs such as CYP1A1 and CYP1A2.[38] Smokers are therefore less exposed to drugs metabolised by these enzymes such as some psychotropics. Another environmental factor known to contribute to variability in drug exposure are pollutants. Drug effects appear to be decreased in workers occupationally exposed for some pesticides and in the urban population. In clinical practice, drug-drug interactions are the most important environmental source for variation.

1.4.2.3 Drug - drug interactions

Drug - drug interactions (DDIs) refer to the event where the administration of one drug affects the course or action of one or several other drugs. An interaction between two drugs can occur at any level from the point of administration to excretion site. Interactions between drugs have in research, as well as in clinical practice, mainly been considered as a pair wise phenomenon. The dominating study designs are experimental where the clinical effect or plasma concentration of one drug is measured before and after the administration of another drug in healthy volunteers.[39 40] Bearing in mind that polypharmacy, among many groups of patients is quite pronounced, there is certainly reason to believe that the basis for interactions between drugs in clinical praxis is far

more complex than that. Interactions between three or more drugs have however been studied to very little extent.[41]

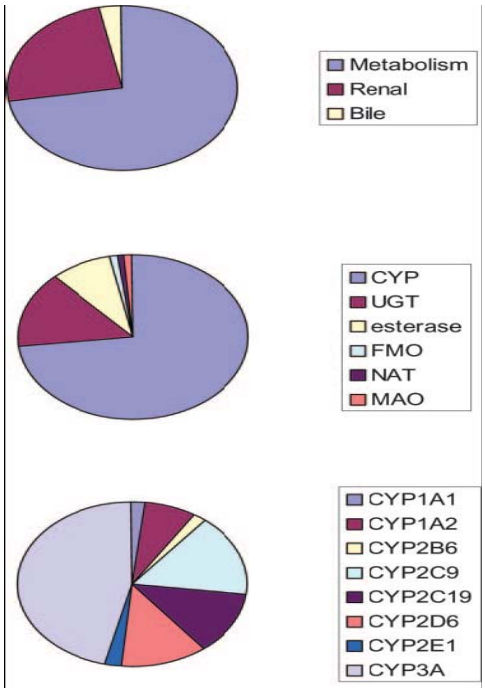
1.4.2.3.1 Frequency and clinical consequences

Although there are many studies that estimate the clinical consequences due to ADRs, data that focus on the effects of DDIs in particular are sparser. Pirmohamed et al. showed in their large prospective study that 1.1% of hospitalisations are associated with DDIs, a figure comparable with other estimations.[5 42] Estimations of the occurrence of potential DDIs, have been assessed in several settings in register based studies. Merlo et al. estimated the frequency of potential DDIs of any clinical significance to 13.6% in a cross sectional study, that included all dispensed drugs in Swedish pharmacies in January 1999.[43] Gregor at al found that 25.53% of SSRI users experienced concomitant use with at least one of the 33 studied CYP2D6 or CYP3A4 metabolised medications in a large register based study in Arizona indicating potential DDIs.[44] A Norwegian study, also register based, found that the frequency of DDIs associated with CYP2D6 and CYP3A4 was 26.3% and 12.5% respectively.[45] Data regarding to what extent awareness of potential DDIs affect drug dispension is however scarce.

1.4.2.3.2 Mechanisms of drug-drug interactions

An interaction where one drug modulates another drugs impact at the site of action, typically by affecting the same receptor, is called a pharmacodynamic drug-drug interaction. An interaction where the time course of tissue levels of one drug in the body is affected by another is called a pharmacokinetic drug-drug interaction. Pharmacokinetic drug-drug interactions affect processes that lead to an altered absorption (A), distribution (D), metabolism (M) or excretion (E) and are therefore also called ADME interactions. Although some hydrophilic drugs are eliminated essentially unchanged in the urine, most drugs, approximately 75%, are transformed into more water soluble compounds before excretion. This is done by two major types of reactions. The Phase I reactions include oxidation, reduction and hydrolysis. They are often followed by the Phase II reactions where another substance, such as glucuronic acid, is conjugated to the transformed drug which hereafter easily can be excreted by the kidney or bile.[46] Although there are several enzymes used for the metabolism of drugs, oxidation mediated by the superfamily of cytochromes P 450 (CYP) dominates. It is estimated to contribute to 50% of the clearance of the 200 drugs mostly used in the United States (Figure 3). The CYPs are divided into families and subfamilies according to a classification system based on the level of amino acid similarity. They are heme-containing membrane bound proteins localised predominantly in the liver but also in other parts of the body. Although there are 18 known families that include about 60 enzymes,[48] only the first three, CYP1, CYP2 and CYP3 are known to contribute to the metabolism of exogenous substances (Figure 3). A drug may affect the activity of a particular CYP which results in a change in the plasma level of a co-dispensed substrate. Inhibition of the catalytic ability will lead to increased plasma levels and increase the risk of dose dependent adverse drug reactions. To co-dispense the beta-blocker metoprolol, which is a substrate of CYP2D6, with paroxetine, a potent inhibitor of the same enzyme, results in increased plasma levels of metoprolol and a subsequent decrease in heart rate and blood pressure.[49 50] In the case of prodrugs, drugs whose

pharmacologic effect demands its metabolism, inhibition might result in an abolished effect. Codeine is one example of a prodrug whose pharmacologic effect depends much on its metabolism to morphine, a reaction also catalysed by CYP2D6. Individuals who were pre-treated with quinidine, another potent inhibitor of the same enzyme, remained essentially unexposed to morphine which resulted in a reduced or absent analgesic effect.[51] As this thesis in particular focuses on interactions associated with the CYP2D6, these will be further discussed below.



Modified from Williams et al., 2004 with permission from the American Society for Pharmacology and Experimental Therapeutics[47]

Figure 3. *Clearance mechanisms for the top 200 drugs prescribed in the United States in 2002. Top panel, listed clearance mechanisms; second panel, listed enzymes contributing to clearance for metabolized drugs; third panel, proportion of cytochrome P450 substrates in the top 200 metabolized by each listed member of that subfamily.*

CYP2D6 belongs to the most important CYPs together with CYP3A4, CYP2C and CYP1A2 with regard to the number of drugs metabolised (Figure 3). The gene coding for CYP2D6 is subject to an extensive genetic polymorphism which explains a large part of the variability in the response of drug treatment for this enzyme's substrates. Between 5-10% of Caucasians thus lack a functional CYP2D6 while 1-3% has three or more copies resulting in ultrarapid metabolism. The remaining individuals have one copy in each of the two chromosomes and are called extensive metabolisers. The substrates of CYP2D6 are mostly basic compounds, many of which act on the central nervous system. Many antipsychotic drugs, antidepressants and sedatives are thus metabolised by CYP2D6. Around 35 different drugs are known to inhibit CYP2D6.[52] Co-prescription of drugs belonging to these different classes is frequent. The SSRIs fluoxetine and paroxetine, who are known to be among the most potent inhibitors, have been shown to increase the plasma concentration of co-dispensed CYP2D6 substrates

several-fold and phenotypically convert extensive metabolisers to poor metabolisers. Their combination with drugs that depend on CYP2D6 metabolism for their clearance or pharmacological bioactivation such as metoprolol or codeine should therefore be avoided or lead to dose adjustments.[53] It is interesting to note that citalopram and sertraline, despite similar therapeutic indication, do not share these properties. Their inhibitory affect on CYP2D6 is only mild and not clinically relevant.[39 54 55] This may be used by the prescriber to avoid potential drug-drug interactions.

There are three ways to avoid a potential interaction between drugs A and B.
1) To change drug A to another drug with a similar therapeutic indication that does not interact with drug B.
2) To change drug B to another drug with a similar therapeutic indication that does not interact with drug A.
3) To change the dose of the drug whose metabolism is potentially affected.

One way to avoid potential CYP2D6 associated drug-drug interactions involving SSRIs, is thus to choose a SSRI that does not inhibit this enzyme, in essence citalopram or sertaline. Another way is to change the drug on the other side of the potential drug-drug interaction to one that does not depend on CYP2D6 for its metabolism or bioactivation. Metoprolol can thus be changed to atenolol, a drug with similar cardiovascular indications but eliminated in an unchanged form by the kidneys and without any significant CYP2D6-dependent metabolism.[56] Codeine can be changed to propoxyphene which similarly to codeine is preferentially used for treatment of mild to moderate pain. Propoxyphene does however not require bioactivation and is metabolised primarily by CYP3A4.[57]
Donepezil and galantamine are acetylcholine esterase inhibitors used for the treatment of Alzheimer's dementia. They are both metabolised by CYP2D6. Exposure-dependent adverse drug reactions, for instance gastrointestinal symptoms, are considered dose-limiting.[59] A therapeutic alternative, in the case of suspected CYP2D6 inhibition is rivastigmine, an acetylcholine esterase inhibitor with similar indications compared to donepezil and galantamine but which is however not metabolised by CYP2D6. It is eliminated unchanged through the kidneys.[59] Tamoxifen is another prodrug used as an adjuvant treatment in oestrogen receptor positive breast cancer. The therapeutic efficacy of tamoxifen is mainly dependent on its metabolism to endoxifen, a reaction catalysed by CYP2D6.[60-62] Anastrozole is also used as an adjuvant treatment in oestrogen receptor positive breast cancer. Anastrozole, is however, not a prodrug but works by direct inhibition of CYP19-dependent steroid aromatization and can therefore be combined with drugs that inhibit CYP2D6 without a risk for a diminished effect.[62 63]

1.4.2.4 Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) refers to a dosing controlled by the measurement of one or sequential drug concentrations in plasma. The presumption for TDM assessment for a certain drug is that the same dose results in differences in plasma levels between individuals which in turn lead to a clinically meaningful difference in effect. Effect may here refer to therapeutic response, or to dose dependent adverse drug reactions. Therapeutic drug monitoring is today routinely assessed for a large number of drugs such as antiepileptics, digoxin and neuroleptics on the demand of clinicians to

monitor its clinical effect. The TDM laboratory in Karolinska University Hospital, Division of Clinical Pharmacology Huddinge is presently offering the determination of plasma levels regarding around 100 drugs. The knowledge concerning the dose – plasma concentration – effect relationship varies largely. Information regarding patient characteristics such as gender, age, smoking, kidney function and concomitant drug treatment is available from the lab-requests that have been accumulated over the years. By combining this information with the obtained plasma concentrations, important questions can be addressed regarding different sources of inter- and intra-individual variation in drug exposure. The neuroleptic risperidone is one drug that is subject for TDM. A look at the rational for TDM of risperidone illustrates some important aspects regarding the interplay between the different factors important for the interindividual differences in drug exposure that need to be taken into account when interpreting its result. As discussed above the interindividual differences in plasma concentration following administration of the same dose is large. The main metabolic pathway for risperidone is hydroxylation to 9-OH-risperidone by CYP2D6. The pharmacological activity and potency of risperidone and 9-OH-risperidone have been claimed to be similar and the sum of the two compounds is often referred to as the "active moiety".[64] A therapeutic window has been proposed to be between 30nM - 80nM. An increased risk for extrapyramidal symptoms has been reported over this range.[65-69]Based on the knowledge that the metabolism of risperidone is mainly dependent on CYP2D6 it is reasonable to believe that a large part of the inter-individual variability is due to genetic polymorphism and co-medication with drugs known to inhibit CYP2D6 which has in fact been confirmed in studies. About 45% of the active fraction is excreted through the kidneys. Elderly and patients with impaired renal function therefore have an elevated plasma concentration.[70] Carbamazepine decreases the plasma concentration of risperidone, probably due to the induction of CYP3A4.[71]

1.4.3 Pharmacoepidemiology

Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people. The field has primarily concerned itself with the study of adverse drug reactions. In Sweden we have a long tradition of world leading register based research due to among other things the use of unique personal identifiers (personal identification number) in the population which makes it possible to link different registers together. Since July 2005, the Swedish prescribed drug register has been in use that documents all prescribed and dispensed drugs in the entire population. Since the information is individual based, thorough investigations of prescribing patterns is feasible.

1.4.3.1 The Swedish prescribed drug register

The Swedish prescribed drug register contains data with unique patient identifiers for all dispensed prescriptions to the whole population of Sweden. As the information is connected to each individual thorough investigations of dispensing patterns is now possible instead of being limited to mean values of drug costs or prescribed daily doses. Data on all dispensed prescriptions is transferred monthly to the Centre of Epidemiology at the National Board of Health and Welfare, which is responsible for keeping the register. The register contains data on drugs dispensed, amounts, dosages,

expenditures and reimbursements, as well as age, gender and unique identifier (personal identification number) of the patient. Unfortunately no clinical information on diagnoses/indications for treatment is recorded.[72]

1.4.4 Medication reviews

One suggested strategy that aims to implement knowledge concerning drug safety is to provide personal expert resources at different levels in health care. These resources can be clinical pharmacologists, pharmacists or nurses and the level of intervention can be hospitals, nursing homes, secondary care or in the homes of selected groups of people. Some studies have been performed to evaluate such interventions with regard to morbidity and mortality. The majority have been unable to show a significant effect.[20] However, Wu et al. performed a randomised controlled trial that showed a marked effect of telephone counselling by pharmacists.[73] A Swedish study was recently published showing a large effect of a more comprehensive intervention, also this performed by pharmacists.[74] A home based medication review resulted in contradictive results leading to a significant increase in hospital admissions. [75] The same author later conducted a review and a meta-analysis that concluded that pharmacy interventions do not have any effect on reducing mortality or hospital admission in older people, and can not be assumed to provide substantial clinical benefit.[76]

1.4.5 Health information technology

Health information technology (HIT) refers to the comprehensive management of health information and its secure exchange between patients, providers, and quality entities. HIT in general are increasingly viewed as the most promising tool for improving the overall quality, safety and efficiency of the health delivery system.[77] Important HITs include Computerised Physician Order Entry (CPOE) and Computerised Decision Support Sytems (CDSS). CPOEs are computer-based systems that share the common features of automating the medication ordering process and that ensure standardised legible and complete orders. Clinical decision support systems are almost always, to some extent integrated in CPOEs to provide computerised basic advice regarding such as choice of drug doses and administration routes. More sophisticated CDSS can perform checks of known allergy, drug evaluation checks and drug-drug interaction checks. In addition, computer-based prescribing systems are the first step to reach the urgent goal of creating a mutual prescribing list that can be shared between different health care providers.

Many CDSS are available for minimising ADRs in general.[58 78] Softwares used to prevent DDIs has an important role.[79-81] But although the notion of the computer as a tool that helps the physician avoid the large number of potential DDIs is appealing, computerised patient management systems for preventing DDIs are not yet used routinely in health care.[82] CDSS have indeed been shown to reduce medication related errors[78 83 84] but do sometimes slow clinicians' work-flow[85] and there are even examples of CDSS introducing new types of errors.[86] Another well-documented problem, particularly concerning software for preventing potential DDIs, is the tendency to produce too many non-significant warnings, leading to non-adherence to

the advice by prescribing physicians due to alert fatigue, a syndrome also known as the "Cry Wolf Syndrome".[87-91]

In Sweden, a comprehensive database has been developed that describes and lists DDIs. It is connected to the Janus Web Application (JWA), a software that presents the information available through the worldwide web. Furthermore, the database is integrated in a more general CDSS called Janus Computerised Prescribing System.[92] For a large number of general practitioners, it is an automated part of the prescribing process warning for potential drug-drug interactions at the point of prescribing. The alert issued by the software included a categorisation of the DDI by clinical significance: *A*) Unlikely to be of clinical importance. *B*) Clinical importance not yet established. *C*) Might result in a changed effect or adverse drug reactions that can, however, be controlled by individual dosage and/or measurement of drug concentration in plasma; the drug combination could require adjustment of the dosage. *D*) Might have severe clinical consequences such as serious adverse drug reactions, loss of effect or otherwise difficult to control with individual dosage; the drug combination should therefore be avoided.[93]

1.5 Aims of the thesis

Study 1
To describe the scenario and frequency of drug-related problems (DRPs) in in-patients and to determine whether a pharmacotherapeutic advisory intervention aiming at reducing DRPs could affect rates of re-hospitalisation and / or death within 6 months.

Study II
To evaluate the clinical relevance of the Janus Web application in screening for potential drug-drug interactions.

Study III
To study drug-drug interactions (DDIs) in patients on polypharmacy, using risperidone as a marker for inhibition of the hepatic cytochrome P450 enzyme 2D6 (CYP2D6).

Study IV
To study whether doctors are taking potential DDIs for serotonin reuptake inhibitors into account in the prescribing decision.

2. METHODS

2.1 Paper 1

Study I was a prospective, randomised, controlled advisory intervention study performed at the medicine clinic at Stockholm Söder Hospital. 305 patients taking 2 drugs or more were included and randomised to either intervention group or a control group. Medical symptoms were estimated by a nurse together with the patient. Creatinine clearance was calculated. Thereafter a clinical pharmacologist scrutinized the patients´ medical records for DRPs that were classified according to the PCNE V4[3] together with the nurse. Clinically relevant DRPs resulted in a written advice to the physician in charge of the patient. The control group received usual care. After 6 months the patients in the two groups were followed up according to the primary endpoints, re-hospitalisation and death.

2.2 Paper II

The 150 patients in the intervention arm in study number 1 were used to evaluate the clinical relevance of the Janus Web Application (JWA) in screening for potential Drug–Drug Interactions (DDIs). Potential DDIs were identified by the JWA The alert issued by the software included a categorisation from A to D of the DDI according to clinical significance.[93] In this paper, significant Potential DDIs are types C and D. Interviewing the patient, and looking into his/her medical records gathered complementing information. A clinical pharmacologist judged which potential DDIs that were clinically relevant. Potentially relevant DDIs identified by the JWA were then correlated with clinically relevant DDIs.

2.3 Paper III

In this investigation, data from Therapeutic Drug Monitoring (TDM) was used to study the impact of multiple CYP2D6 substrates and inhibitors on plasma risperidone levels. Information concerning patient and sampling details with special regard to concomitant medication was extracted from the lab-requests and correlated with the analytical results on plasma concentrations of risperidone and 9-OH-risperidone in 218 patients.

2.4 Paper IV

The purpose was to study the management of important drug-drug interactions (DDI) in clinical practice. It was hypothesized that doctors would avoid prescribing drugs that depend on cytochrome P450 2D6 metabolism for elimination or pharmacological activation (CYP2D6-drugs) together with SSRI antidepressants that block the activity of CYP2D6.
This was a retrospective, cross-sectional analysis of individual dispensing for the prescription drugs under study. Four months dispensing data during for all individuals in the Swedish population, 15 years and older (n= 7713945) were analysed. The use of "*CYP2D6-drugs"* (metoprolol, donepezil, galantamine, codeine, tamoxifen) together with CYP2D6-blocking SSRIs (paroxetine, fluoxetine) or SSRIs that do not block

CYP2D6 (citalopram, escitalopram, sertraline) was analysed, and related to the use of CYP2D6-independent *comparator drugs* (atenolol, rivastigmine, propoxyphene, anastrozole).

2.5 Statistics

In paper I the Chi-square test was used to test the differences in proportion of re-hospitalisation or death between the intervention and the control group at 6 months. In paper II, a simple correlation matrix was used to investigate the association between potentially relevant DDIs identified by the JWA and DDIs that resulted in a written advice. To compare the concentration-to-dose (C/D) ratio of risperidone between patients treated with different numbers of concomitant CYP2D6-related drugs (0, 1, >1) we used the Kruskal-Wallis test. The Mann-Whitney U-test was used to test the difference between two groups. P-values <0.05 were regarded as significant. In paper IV, multiple logistic regression was used to examine the importance of the type of SSRI for the choice of therapeutic drug and to control for confounders.

3. RESULTS

3.1 Paper I

The baseline characteristics in the two groups of patients were similar. The mean age in the control group and intervention group was 74 and 71 years respectively. A total of 299 DRPs among 71% (106/150) of the patients were found, who had not previously been identified in the usual care. Thirty-five per cent (106/299) of DRPs in 39% (58/150) of the patients were judged to be of such importance that advice was given to the physician in charge. The most common advices were “information” (36/106) followed by “cease drug” (33/106), “reduce dose” (20/106) and “change of drug” (13/106).

After 6 months, the number of re-hospitalisations and deaths were counted. The proportion of re-hospitalisation and death in the intervention group was 49% (73/150) compared to 46% (69/150) in the control group (Risk ratio: 1.06, 95% confidence interval: 0.84 to 1.32, P=0.64). The number of re-hospitalisations and deaths were also counted separately. The proportion of deaths in the intervention group was 19% (29/150) compared to 15% (22/150) in the control group (risk ratio: 1.19, 95% confidence interval: 0.85 to 1.67, P=0.28). The number of patients who were readmitted to hospital one or more times was 40% (60/150) in the intervention group compared to 35% (53/150) in the control group (risk ratio: 1.11, 95% confidence interval: 0.87 to 1.41, P=0.40).

Twenty-two per cent (33/149) of the patients had a creatinine clearance <35 ml/min. Thirty-four per cent of the DRPs (103/299) and 30% of the advice given (32/106) were associated with this group of patients. There was no obvious over-representation of advice in patients with decreased kidney function. Many in this group of patients were taking drugs mainly excreted by kidney and/or drugs potentially nephrotoxical such as diuretics (37 patients), ACE-inhibitors (9 patients) or digoxin (3 patients).

3.2 Paper II

We found 251 potential DDIs in the 150 patients that were studied. One hundred and fifty DDIs, regarding 58 different interaction pairs, were classified as significant, that is, type C or D. Of these, 24 resulted in written advice and were hence judged to be relevant in the specific clinical context. Information regarding how the physicians complied with the advices was received in 19 out of 24 cases. Thirty-seven percent (7/19) of the advices were followed by the physician in charge of the patient. The individual screening by the clinical pharmacologist did not result in any written advices concerning DDIs that were not identified by the JWA.

The other 126 interactions that were significant by definition did not result in advice. The drugs that were most frequently associated with potential DDIs classified as type C or D without resulting in written advice were ACE inhibitors, diuretics, antidiabetics and drugs for treatment of obstructive pulmonary disease.

3.3 Paper III

The median C/D ratio of risperidone in patients with 0, 1 or >1 was 2.6, 8.5, and 17 nmol/L/mg, respectively. The difference between all three groups was highly significant ($p<0.001$). The "active moiety" (risperidone + 9-OH-risperidone), in patients with different numbers of concomitant CYP2D6 inhibitors was 17, 24 and 30 nmol/L/mg, respectively ($p<0.01$). Differences in "active moiety" between the groups were exclusively explained by an accumulation of risperidone in the presence of CYP2D6 inhibitor(s), while plasma concentrations of the metabolite 9-OH risperidone were similar with or without inhibitor(s). The prescribed daily doses of risperidone did not differ between the three groups.

To compare the effect of individual inhibitors on C/D ratio of risperidone, we determined the C/D ratio in the presence of each individual inhibitor in the 57 patients with only 1 inhibitor. Patients exposed for thioridazine, paroxetine and levomepromazine, were associated with the highest C/D ratio of risperidone (24, 19 and 12 nmol/L/mg respectively). All of the medication lists in the 7 patients with >1 inhibitor of CYP2D6, included fluoxetine, paroxetine, thioridazine and/or levomepromazine, i.e. drugs known as potent inhibitors of CYP2D6.[33 94 95]

3.4 Paper IV

The mean age in the study population (n=7713945) was 47 years, and 51% were women. The numbers of individual patients in the whole population that were dispensed fluoxetine/paroxetine together with metoprolol, donepezil, galantamine, codeine and tamoxifen were 3164, 158, 61, 2322 and 131, respectively. Compared with patients who where dispensed citalopram/sertraline, patients dispensed fluoxetine/paroxetine faced a reduced risk of receiving metoprolol (adjusted odds ratio, 0.80; 95% CI, 0.76 to 0.85), donepezil (0.65; 0.49 to 0.86) and galantamine (0.58; 0.41 to 0.81). In contrast, the risk of receiving codeine (instead of propoxyphene) or tamoxifen (instead of anastrozole) was similar among patients on fluoxetine/paroxetine compared to citalopram /sertraline (adjusted odds ratios, 1.03; 95% CI, 0.94 to 1.12 and 1.29; 95% CI, 0.96 to 1.73 respectively). The volumes of dispensed Defined Daily Doses (DDD) of all study drugs were similar in patients on the different SSRIs.

4. DISCUSSION

4.1 Paper I

We found in average 2.0 DRPs per patient (299/150) in 71% (106/150) of the patients in the intervention group. These figures are comparable with a Norwegian study from 2004 where the equivalent figures were 2.1 and 81%.[96] Twenty two percent of this elderly group of patients suffered from an impaired function of the kidney with a creatinine clearance below 35 ml/min, a level commonly regarded as critical for drugs eliminated through excretion by the kidney. Many individuals were taking medication mainly excreted by the kidney and/or being potentially nephrotoxic. Three of the patients with a creatinine clearance <35ml/min had a normal S-creatinine which shows the importance for physicians to make the extra effort of estimating the patient´s creatinine clearance using a formula based on the patients´ weight, sex and age in addition to S-creatinine.[30] However, there was no obvious over-representation of advice regarding patients with decreased kidney function. Many physicians were probably aware of the importance of decreasing the drug dose in this group of patients.

The present study was not only descriptive but also a part of an intervention investigating whether pharmacatherapeutic advices could reduce morbidity or mortality. The proportions of re-hospitalisations and deaths in the intervention group and the control group after 6 months were similar. There are numerous studies showing that the prevalence and consequences of ADRs are large and that most of them are preventable. The main problem with these studies is that the classifications are based on a number of soft clinical judgments (Table 1). It may therefore be difficult to estimate the true magnitude of the clinical effects of preventable ADRs. Figure 4 shows the classifications of ADRs in a very well performed, large, prospective study that aimed to determine the burden of drug related morbidity among 18820 patients admitted for hospitalisation.[5] In 1225 cases (6.5%), the admissions were judged to be due to an ADR of any type, according to the definition by Edwards et al.[15] In 980 (80%) of the cases, the ADR was judged to be directly responsible for the admission. The causality assessment according to Karch et al.[19] resulted in that 865 of the ADRs were classified as definite or probable while 360 were classified as possible, due to a smaller probability of a casual association. Warfarin is among the drugs most commonly associated with serious ADRs.[5 10] On the other hand it is a well established fact that warfarin, which is known to be the most effective stroke preventive medication in patients with atrial fibrillation in combination with characteristics associated with an increased risk of thromboembolism, such as high age, is underused.[97] This paradox illustrates the need to integrate a benefit – risk estimation when evaluating the effects of drug related problems in a population. This is formally done by assessing avoidability and thereby judge whether the management of the patient had been compatible good medical practice (Table 1). Avoidability is unfortunately often not assessed in studies aiming to describe the burden of ADRs.[2 10] Pirmohamed et al. did however do so using the definition by Hallas et al.[17] Of the 1,225 hospital admissions that were related to any kind of ADR, they found that 9% and 63% were judged as "definitely avoidable"and "possibly avoidable" respectively and concluded: "Thus we classified 72% of ADRs as avoidable." In summary, it is very difficult to estimate the proportion of avoidable hospitalisations due to drug-related problems in descriptive studies. A

conservative calculation based on the proportion of ADRs judged to be directly responsible for the admission, where possible ADRs are excluded and only unavoidable ADRs are included, would result in an estimation of 0.8% (Figure 4).

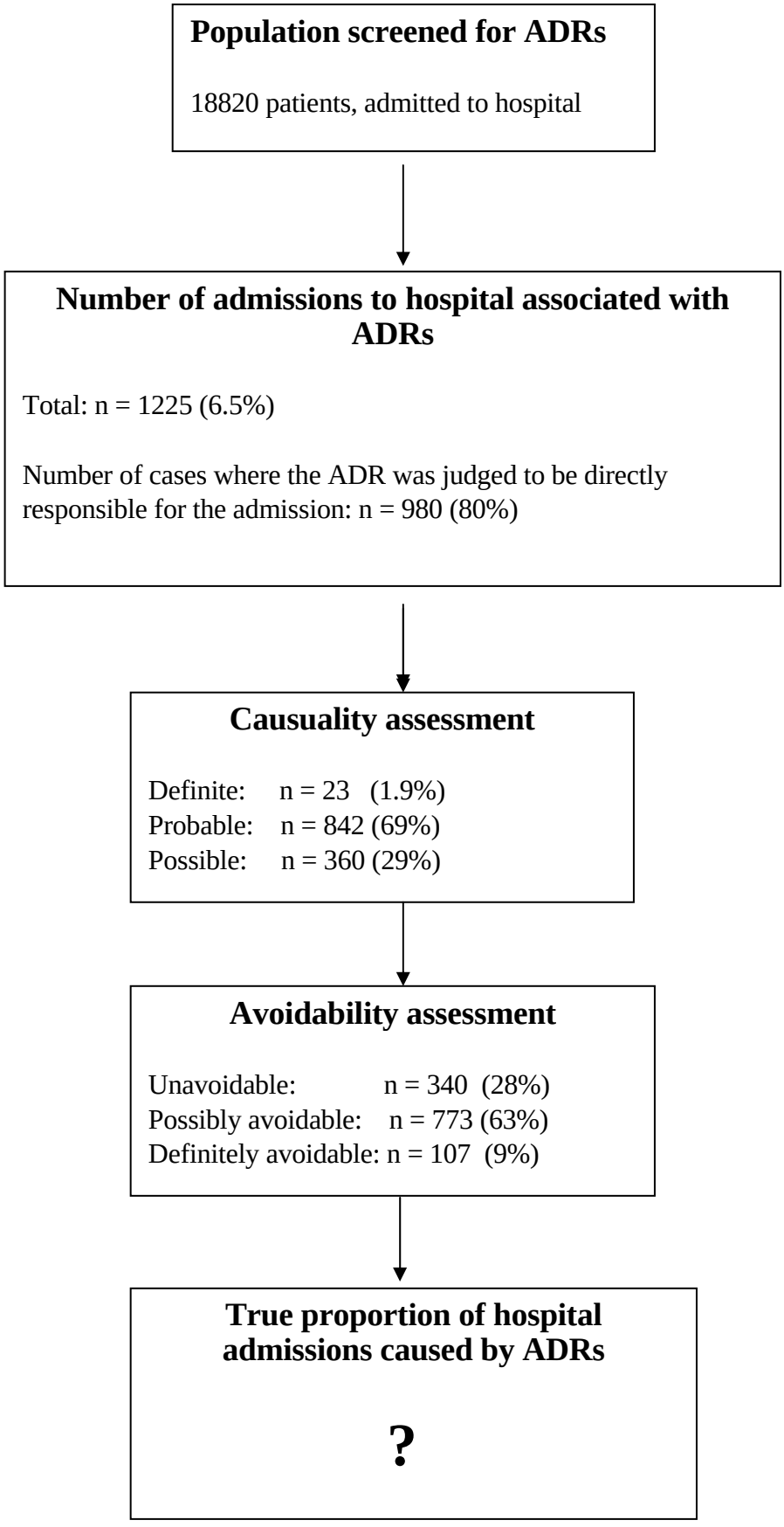


Figure 4. *Assessment of causuality and avoidability in 18820 patients that were screened for adverse drug reactions in the study by Pirmohamed et al.*[5]

One way to get more reliable estimations of the burden of preventable ADRs in a particular population would be to measure the results of an intervention with the purpose to remove the effects of drug-related problems. In paper 1 we actually aimed for this. A limitation regarding the interventional part of the study was however the dimensioning. We aimed at a reduction in the proportion of re-hospitalisations or deaths from 46% to 30.4%, a difference that was rather large. As the results turned out to be negative, our conclusions were accordingly quite weak. The data concerning the effect of medication reviews on hard endpoints are relatively sparse. Most studies have like ours been relatively small and the absolute majority have failed to show a positive effect although there are exceptions.[73-76] In the future should therefore intervention studies that are large enough to detect their true effect in terms of long and short term morbidity and mortality be performed.

4.2 Paper II

We found many potential interactions that by definition were classified as significant (type C or D) but only a few were considered to be sufficiently important to warrant a written advice. A look at the drugs which featured most frequently in such combinations illustrates the nature of this discrepancy. ACE inhibitors, diuretics and antidiabetics contributed 43% of the total number of drugs involved in type C interactions that *did not* lead to advice. The vast majority of these interactions involved ACE inhibitors interacting with diuretics and antidiabetics, respectively. The interaction of ACE inhibitors and furosemide tends to reduce furosemide's natriuretic and diuretic effects. However, as this widely and generally accepted drug regime involves titration of the diuretic up to the optimal clinical effect, in most cases the clinical relevance of the interaction is questionable. It may be more adequate to warn for the well-documented risk of kidney failure. ACE inhibitors also interact with antidiabetics, with an increased risk of hypoglycaemia. This combination is likewise consistent with medical practice, though awareness of the potential DDI may be relevant in particular cases. Nearly all (22/26) of the potential type D interactions, which essentially should be avoided, were not considered to be sufficiently important to warrant written advice. More than half of them (12/22) involved the combination of ipratropium and salbutamol. These results do not imply that the majority of warnings should not have been issued. But it is an aspect that needs to be taken into account when designing the alerts.

The Swedish Finnish drug Interaction X-referencing (SFINX) is another drug-drug interaction database which development was based on a cooperation between the Karolinska Institute, Department of Clinical Pharmacology in Stockholm, Sweden, the Division of Drug Management and Informatics at Stockholm Sweden and The University Hospital in Turku Finland.[98] A comparison between the JWA and SFINX highlights some important issues. When the same medication lists were screened by SFINX, 298 warnings were found, an even higher number that the corresponding figure of 252 when using JWA (unpublished data). When analysing the warning pattern it became clear that alerts concerning common potential interactions had been integrated in the new database that were not recognised in JWA. However, most warnings that in the JWA appeared inadequate were in SFINX not present at all, or presented in a better way. One illustrative example of the difference between the softwares regards the alert

for the combining of ipratropium and salbutamol. Twelve of the 22 type D warnings issued by JWA that did not lead to an advice involved this interaction. Even though there is evidence in terms of case reports that indicate that this combination should be used with caution in the rare cases with patients that are predisposed for angle-closure glaucoma (Figure 5), the combination is consistent with medical practise. It is even available in a one-dose container often used in the treatment of patients with acute exacerbation of chronic obstructive lung disease or asthma. Without further explanation this warning is therefore not optimal for the intern at the emergency unit or for the general practitioner.

Figure 5. *The alert concerning the potential drug-drug interaction salbutamol-ipratropium according to how it appears in the JWA.*

In SFINX, this interaction of drugs is labeled as type C, meaning that the drugs could be administered together if taking certain measures. More important, it explains the background for the warning and includes a piece of advice of how to handle those rare cases that actually are predisposed for angle-closure glaucoma – usage of goggles preventing the evaporated fluid to reach the eye (Figure 6a). For the physician in need for further information, there is a link providing more extensive information labeled “read more” with literature references through which the information can be evaluated (Figure 6b).

C salbutamol - ipratropium

Medical Consquence
Acute angle closure glaucoma have been reported when ipratropium and salbutamol have been administered together. At least one of the substances has been given vaporised by a nebulisator.

Recommendation
Salbutamol och ipratropium should not be given together vaporised by a nebulizer to patients with a medical history of angle closure glaucoma. Alternatively swim goggles can be used. If symptoms of deterioration of vision and or ocular pain occurs, the patients should be referred to an eye specialist.

Read more

Figure 6a. *The alert concerning the potential drug-drug interaction salbutamol-ipratropium according to how it immidiately appears in SFINX. The layout and text have been modified in order to fit editing and presentation purposes.*

C salbutamol - ipratropium

Medical Consequence
(see above)
Recommendation
(see above)

Mechanism
Ipratropium dilates the pupil and blocks the flow of aqueous humor from the posterior to the anterior chamber. Salbutamol might increase the formation of aqueous humor. The effect is probably due to leak of vapour from the facemask and a topical effect on the eye.

Background
Ten cases of acute angle closure glaucoma have been reported when ipratropium and salbutamol have been administered together. In all cases except one, the drugs have been given together vaporised by a nebulizer. In the other one, nebulised ipratropium was given and salbutamol was given by a metered dose inhalator. In three of these cases the patients had one or more prior episodes of acute angel closure glaucoma. In a controlled double-blind crossover study, the effect of ipratropium and salbutamol on intraocular pressure was measured in 36 patients with glaucoma and chronic bronchitis. When the drugs were given together intraocular pressure increased in patients with angle closure glaucoma but not in patients with open-angle glaucoma or in controls. When the combination was administered to patients with angle closure glaucoma wearing swim goggles, no increase in intraocular pressure was measured and no increase was measured in those patients when treatment for glaucoma was used during the whole test period.

References
Lellouche N, Guglielminotti J, de Saint-Jean M, Alzieu M, Maury E, Offenstadt G. [Acute glaucoma in the course of treatment with aerosols of ipratropium bromide and salbutamol]. Presse Med. 1999 May 22-29;28:1017.

Figure 6b. *The appearance of the same alert after the user having clicked the "read more"button". The layout and text have been modified in order to fit editing and presentation purposes.*

4.3 Paper III and IV

In study number III and IV, DDIs related to CYP2D6 was addressed from two different perspectives. In paper number III, we used therapeutic drug monitoring (TDM) data to investigate the ability of different drugs to inhibit this enzyme using risperidone as a marker for CYP2D6 activity. In paper number IV, we applied an epidemiological perspective to investigate the frequency of CYP2D6 related drug-drug interactions in the Swedish population, and how they affect prescribing and dispensing of drugs.

In paper number III, we showed that a number of potent CYP2D6 inhibitors increase the dose adjusted plasma exposure of the sum of risperidone and 9-OH-risperidone, also referred to as the "active moiety" of risperidone at steady state. This confirms previous studies that do indicate that fluoxetine as well as paroxetine increase the "active moiety" risperidone. We found that patients with more than one CYP2D6 inhibitor had higher levels of risperidone than patients with only one inhibitor. However, all of the 7 patients with more than one inhibitor were exposed to either fluoxetine, paroxetine, and or levomepromazine, drugs known to be potent inhibitors of CYP2D6.[33 94 95] Consequently it was in our material not possible to differ between the multi-interaction effect, and the effect of the different individual inhibitors.

TDM is a powerful tool enabling the prescriber to tailor drug treatment for different individuals in order to avoid adverse drug reactions and to optimise the therapeutic effect. TDM can, as we have seen, also be used to retrieve knowledge regarding different sources of variation that can be used to help the prescribers to predict plasma drug exposure without actually having to measure it. The use of daily dose adjusted plasma concentration of risperidone was shown feasible in elucidating the inhibiting effect of different drugs and combinations of drugs. The aim to investigate the effect of multidrug interactions on CYP2D6 level was however hampered by the lack of sufficient number of patients on 3 or more drugs that inhibit this enzyme. To take advantage of the routinely determined plasma concentrations and to correlate them with information regarding co-medication derived from the lab-requests or by linkage to national prescribed drug registers has a large potential. It has a large potential, not only to give highly powered information about interactions between 2 drugs, but also important, to provide information about different types of multi-drug interactions.

As shown in paper III, the SSRIs fluoxetine and paroxetine diminishes CYP2D6 dependent metabolism substantially which can lead to dose related adverse drug reactions or a decrease in therapeutic effect when combined with drugs that need this enzyme for metabolism also including bioactivation. In paper IV, we used the Swedish prescribed drug register to determine the prevalence of five potential SSRI related drug-drug interactions in the Swedish population. More importantly, we obtained results that revealed interesting differences regarding the prevalence of specific drug combinations related to CYP2D6-dependent drug metabolism. Patients treated with an SSRI that block CYP2D6-activity, faced a significantly lower risk to be co-dispensed a CYP2D6-substrate for which the accumulation may lead to symptomatic adverse drug reactions (metoprolol, donepezil and galantamine). However, the choice of SSRI did not significantly influence the risk of being prescribed a drug that requires CYP2D6-dependent bioactivation (tamoxifen and codeine).

Even though DDIs are regarded as a major health care problem, data on how DDIs can affect drug utilization is very scarce. This study opens a number of possibilities for important research.

Firstly it is urgent to determine the cause for the difference in prescribing of acetylcholine esterase inhibitors and metoprolol in patients with different SSRIs. Whether or not these risks have been considered prior to initiating treatment with the CYP2D6-drug or CYP2D6-inhibitor remains unclear. For example, the relative imbalance towards the use of atenolol rather than metoprolol in patients co-medicated with CYP2D6-inhibitors might result from patients starting on metoprolol but subsequently switching to atenolol upon difficulty to reach target dosing due to bradycardia and hypotension. Alternatively, this reflects a clinical awareness of the risk of adverse drug reactions when combining metopolol with potent CYP2D6 inhibitors, and a corresponding rational choice in drug prescription. These questions should be addressed by the use of a longitudinal approach studying the dispensing pattern of each individual over time.

2322 individuals in Sweden on codeine were similarly dispensed fluoxetine or paroxetine, and were therefore exposed for a risk of an absent analgesic effect. It is remarkable that the odds ratio for the use of codeine in patients in this group of patients was not lower, than among patients on sertraline or citalopram. There are at least four possible explanations/implications for this; 1) a lack of analgasic effect that may not be properly evaluated in this vulnerable group depressed patients, 2) a compensatory increase in the consumption of other analgesics including paracetamol and/or cyclooxygenase inhibitors, 3) poor compliance and reduced or irregular intake of the CYP2D6-blocking antidepressant, 4) the clinical relevance of this interaction may be smaller than previously believed.

There is quite strong evidence that the analgesic effect of codeine is reduced or abolished of administered together with a potent inhibitor of CYP2D6.[51] However, in the absence of other explanations, this position may need to be revaluated. Register based research may thus provide indirect evidence for or against clinical relevance for interactions. The imbalance in the dispensing of donepezil and rivastigmine is another example of such indirect evidence. Even though drug label guidelines as they are expressed in the Swedish Physicians' Desk Reference (FASS) warn against combining donepezil with inhibitors of CYP2D6, these warnings are quite subtle saying that these combinations should be used “with caution”.[53] Still, the results suggest a marked discrimination of donepezil in favour of rivastigmine in patients that are co-dispensed fluoxetine or paroxetine. If a longitudinal investigation show that physicians do not take this interaction in consideration a priori, this would provide further evidence for a clinical relevant interaction.

The risk of impaired therapeutic efficacy of tamoxifen during combined treatment with CYP2D6-blocking SSRI is today discussed in the paroxetine drug label, but neither in the corresponding label for fluoxetine, nor the tamoxifen label itself. It would be of great interest to follow the possible impact of label changes in this respect. The current data do however indicate that 131 Swedish women will have very little clinical benefit

from tamoxifen due to the combined treatment with fluoxetine or paroxetine. It would certainly be of interest to investigate what the exposure of this interaction means for the risk of relapsing in breast cancer.

The design of this study is conceptually original and could be applied on other important types of DDIs than those caused by inhibition of CYP2D6. Thus it would be interesting to study how drug-drug interactions associated with other "problem areas" such as warfarin treatment affect drug dispensing.

4.4 Future outlook

Computerised decision support that integrates knowledge concerning different aspects of drug safety into clinical practice will definitely play an important role in tomorrow's health care. Some argue that technologies for computer order entry and decision support even today is sufficiently mature for broad implementation in at least large hospitals[82] while others believe that the negative effects still overwhelms the positive ones.[99] The DDI area should be highly appropriate for decision support, considering the complexity of drug treatment and the immense number of potential drug-drug interactions. To address the "Cry Wolf Syndrome" caused by too many non-significant inadequately displayed "red alerts" desensitising the prescribers, constitute an absolute prerequisite in this regard.

Even though not yet evidenced based, my personal view is that medication reviews are valuable. In a broad sense, reviewing patients' medication lists is and will always be a mutual responsibility for all health care providers. Apart from being intuitively useful for the patients that are reviewed, more formal medication reviews have a pedagogic value indicating problem areas in the specific local context in which they are performed. They may also have an impact on soft measures that may be hard to estimate such as quality of life.

4.5 Conclusions

Paper I shows that drug-related problems are common. The impact of drug-related problems on hard endpoints such as re-hospitalisation and death may however be overestimated. It is of importance to clarify if and in what way drug-related problems are preventable.

Paper II shows that the absolute majority of the advices issued by the JWA was not relevant in the particular clinical context. With the aim to develope a drug-drug interaction software with the goal of achieving and maintaining a general use on a routine basis, it is of great importance that the alerts are clinically relevant. Equally important may be to present the warnings in an adequate way to give the prescribing physician a balanced picture of the problem and thereby avoid "alert fatigue".

Paper III shows that an increase in the number of concomitant inhibitors may be associated with a lower CYP2D6 activity, although the type of inhibitor is probably more important. Drug-dependent inhibition of CYP2D6 increases the "active moiety" of risperidone. An indication for risperidone TDM should consequently include concomitant medication with established CYP inhibitors.

Paper IV suggest that 'silent' DDIs related to reduced bioactivation of prodrugs might be more easily neglected in clinical practice, as compared to DDIs that cause drug accumulation and overt ADRs. This indicates a need for improved compliance to drug label recommendations and also a need for continuous medical education about the basic pharmacology of commonly used drugs.

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