From the Department of Laboratory Medicine
Division of Clinical Pharmacology
Karolinska Institutet, Stockholm, Sweden

DRUG-DRUG INTERACTIONS – FROM KNOWLEDGE BASE TO CLINICAL IMPACT

Marine Andersson

Karolinska Institutet

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"To kill an error is as good a service as, and sometimes even better than, the establishing of a new truth or fact."

Charles Darwin

"A day without laughter is a day wasted."

Charlie Chaplin

ABSTRACT

Drug usage has increased steadily, and the more drugs used, the higher the risk for adverse effects or loss of effect due to drug-drug interactions. For drug prescribers it is difficult to know what drugs a patient is taking and whether they interact. Computerizing of health care records has made it possible to connect patients' drug lists to clinical decision support systems giving the prescriber information about e.g. drug-drug interactions, duplicated prescriptions and drugs in pregnancy. The aim of this thesis is to create a knowledge base suitable for usage in decision support systems, to evaluate the database in clinical practice, and to use existing clinical databases to create new knowledge about possible drug-drug interactions and their mechanisms.

Paper I is a description of how the knowledge base SFINX was created. The publication describes handling of substances and drug formulations. Standardization of literature searches and text formulations, classification of interactions, structuring of interaction texts, basis for recommendations and the process of approval is also discussed.

In paper II, the interaction between lamotrigine and quetiapine was studied using therapeutic drug monitoring data. Patients exposed to both quetiapine and lamotrigine were matched with controls exposed to quetiapine alone. The dose-corrected quetiapine concentration was 58% lower in patients co-treated with lamotrigine than in patients treated with quetiapine alone, possibly due to induction of quetiapine metabolism by lamotrigine.

In paper III, the influence of mutations in the CYP2C9 gene on the interaction between simvastatin and warfarin was studied. In patients with a CYP2C9*3 allele, the warfarin maintenance dose was 25% lower if treated with simvastatin, according to the results from multiple regression. No significant interaction could be observed in patients lacking the *3 allele.

Paper IV was a questionnaire study where we collected information about how SFINX is used and how the database is perceived by the users of the web version. We found that the database is often used when the prescriber/pharmacist sees the patient, that the information influences the treatment of the patient, and that the database is used to learn more about interactions.

In paper V, we investigated if integration of SFINX into electronic health care records prevented the prescribing of drug combinations leading to potentially serious drug-drug interactions in primary health care. When comparing prescriptions between a period before integration of SFINX and a period after integration, we found that the prevalence of potentially serious drug-drug interactions decreased significantly by 17%.

SAMMANFATTNING

Läkemedelsanvändningen har ökat stadigt och ju fler läkemedel som används desto större är risken för läkemedelsinteraktioner som kan leda till biverkningar eller utebliven effekt. För den som skriver ut läkemedel är det väldigt svårt att veta dels vilka läkemedel patienten tar, dels om dessa interagerar med varandra. Datorisering av patientjournaler gör det möjligt att koppla patientens läkemedelslista mot så kallade förskrivarstöd som ger förskrivaren information om t.ex. läkemedelsinteraktioner, dubbelförskrivningar och läkemedel under graviditet. Syftet med denna avhandling är att utveckla en kunskapsdatabas om läkemedelsinteraktioner, lämplig att använda i förskrivarstöd, att utvärdera databasen i klinisk praktik, samt att använda befintliga kliniska databaser som grund för att skapa ny kunskap om möjliga läkemedelsinteraktioner och mekanismer för dessa.

Det första delarbetet beskriver hur kunskapsdatabasen SFINX skapades. Artikeln beskriver hur substanser och beredningsformer hanteras. Vidare beskrivs standardisering av texter, hur interaktionerna klassificeras samt arbetet med att skapa dokumentation för sökningar av litteratur och godkännande av interaktionstexterna.

I delarbete II studerades interaktionen mellan lamotrigin, ett antiepileptikum, och quetiapin, ett antipsykotikum, med hjälp av data från rutinmässigt utförda mätningar av läkemedelskoncentrationer. Patienter exponerade för quetiapin och lamotrigin matchades med kontroller enbart exponerade för quetiapin. Koncentration-doskvoten för quetiapin var signifikant lägre hos de patienter som även behandlats med lamotrigin. Den doskorrigerade quetiapinkoncentrationen befanns vara 58% lägre än hos patienter som ej behandlats med lamotrigin, vilket kan tolkas som att lamotrigin inducerat nedbrytningen av quetiapin.

I delarbete III studerades om mutationer i genen för CYP2C9, det viktigaste enzymet för nedbrytning av warfarin, påverkar interaktionen mellan simvastatin och warfarin. Hos patienter med en *3 allel var dosbehovet av warfarin 25% lägre om de behandlades med simvastatin enligt den multipla regressionen. Ingen signifikant interaktion kunde ses hos patienter som saknade *3 allelen.

Delarbete IV var en enkätstudie där vi samlade information om hur SFINX används och hur databasen uppfattas av användarna av webbversionen. Vi fann att databasen ofta används när förskrivaren/farmaceuten möter patienten, att informationen påverkar handläggning av patienten och att användarna använder databasen för att lära sig mer om interaktioner.

I delarbete V undersöktes om införandet av SFINX i journalsystemet minskar primärvårdens förskrivning av läkemedelskombinationer som leder till potentiellt allvarliga interaktioner. Baserat på förskrivningar under en period innan införandet och en efter fann vi att förekomsten av potentiellt allvarliga interaktioner minskade med 17% i den grupp som fått tillgång till SFINX.

LIST OF PUBLICATIONS

This thesis is based on the following publications. The articles will be referred to in the text by their roman numerals.

I. Böttiger Y, Laine K, **Andersson ML**, Korhonen T, Molin B, Ovesjö ML, Tirkkonen T, Rane A, Gustafsson LL, Eiermann B. SFINX-a drug-drug interaction database designed for clinical decision support systems. Eur J Clin Pharmacol. 2009;65(6):627-33

II. **Andersson ML**, Björkhem-Bergman L, Lindh JD. Possible drug-drug interaction between quetiapine and lamotrigine - evidence from a Swedish TDM database. Br J Clin Pharmacol. 2011;72(1):153-6

III. **Andersson ML**, Eliasson E, Lindh JD. A clinically significant interaction between warfarin and simvastatin is unique to carriers of the CYP2C9*3 allele. Pharmacogenomics. 2012;13(7):757-62

IV. **Andersson ML**, Böttiger Y, Bastholm-Rahmner P, Ovesjö M-L, Vég A, Eiermann B. Evaluation of usage patterns and user perception of the drug-drug interaction database SFINX. *Submitted.*

V. **Andersson ML**, Böttiger Y, Lindh JD, Wettermark B, Eiermann B. Impact of the drug-drug interaction database SFINX on prevalence of potentially serious drug-drug interactions in primary health care. Eur J Clin Pharmacol. 2013;69(3):565-71

CONTENTS

LIST OF ABBREVIATIONS

C:D	Concentration/dose
CDSS	Clinical decision support system
CYP	Cytochrome P-450
DDI	Drug-drug interaction
EMA	European Medicines Agency
FASS	Swedish catalogue of approved medical products
FDA	Food and drug administration
HMG-CoA	3-hydroxy-3-ethylglutaryl-coenzyme A
MAO	Monoamino oxidase
NSAID	Non-steroidal anti-inflammatory drug
OATPB1B	Organic anion transporter protein B1B
OCTs	Organic anion transporters
P-gp	P-glycoprotein
SFINX	Swedish Finnish Interaction cross-referencing
SPC	Summary of product characteristics
TDM	Therapeutic drug monitoring
UGT	UDP-glucuronyltransferases
VKORC1	Vitamin K epoxide reductase subcomplex 1
WARG	Warfarin genetics

1 INTRODUCTION

1.1 HISTORY

People have tried to cure diseases with remedies since prehistoric time. In the early days, remedies were usually from herbs or animals. Chemically pure drugs were introduced in the 1920s [1], and since then usage and knowledge about drugs have increased rapidly. It would take 25-30 years after purified drugs were introduced until it became known that drugs can influence the effect of each other.

Cases of a remarkable interaction between monoamino oxidase (MAO) inhibitors, used for depression, and tyramine rich food were published in 1963 [2;3]. Hypertensive crisis starting half an hour up to two hours after ingestion of mature cheeses, such as cheddar, was reported in nine patients. At the time of these reports, the mechanism for this interaction was unknown, but soon it was discovered that the metabolism of tyramine, in the cheese, was inhibited by the antidepressants, causing the observed symptoms [4].

Some years before the MAO-inhibitor interaction was described, unexpected drug interactions causing adverse effects such as hypoglycemia in phenylbutazone (also known as butazolidine [5] and tolbutamide treated patients [6], and increased anticoagulation in phenprocoumon treated patients [7] were reported. In 1956, a single case study was published where the exposure to ethyl biscoumacetate (tromexan, an old coumarin anticoagulant) was increased two-fold by concomitant therapy with phenylbutazone. The same authors also reported being aware of over fifty cases of increased anticoagulative effect of phenprocoumon in patients treated with phenylbutazone [7]. Later it was shown that phenylbutazone is an inhibitor of cytochrome P-450 2C9 (CYP2C9) [8], the enzyme responsible for metabolism of tolbutamide [9] and partially involved in the metabolism of phenprocoumon [10]. It is likely that this may have been the mechanism behind the interaction between ethyl biscoumacetate and phenylbutazone. In 1963, it was demonstrated that the CYP2C9 inhibitor [11] sulphapenazole increased the blood concentration of the oral antidiabetic tolbutamide in three patients [12].

After these initial findings, the knowledge of drug interactions increased rapidly. It was found that many drugs may induce or inhibit the metabolism of other drugs [13;14]. Studies on monozygotic and dizygotic twins revealed that genetics influences drug exposure [15-17]. Knowledge of cytochrome P-450 enzymes and their importance for drug metabolism was discovered [18]. In vitro methodology was improved, and drug-drug interaction studies were performed both humans and in animals.

In 1970, the Swedish authorities required pharmaceutical companies to give annual updates regarding drug interactions in the Swedish catalogue of approved medical products (FASS) [19]. This made drug interaction information much easier for the prescribers to access, but the clinical relevance of the interactions was almost impossible to ascertain. In 1997, a system classifying drug interactions according to clinical relevance and level of documentation was introduced in FASS [20]. This information was later made electronically available, and was used as the base for the

first Swedish electronic drug interaction database published on the Internet. It also was made available in the decision support system Janus toolbar [21].

Today, both the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have clear guidelines [22;23] on how to perform drug interaction studies before market approval and often require additional studies. Still prescribers need to evaluate the clinical relevance of interactions mentioned in the summary of product characteristic (SPC), since much of the information is based on in vitro data only. Furthermore, SPC texts have been shown to include only 33% of the drug interactions described in the literature [24]. Drug interaction warning systems are available, but the information found in different sources varies greatly as does the structure of the systems.

1.2 BASIC CLINICAL PHARMACOLOGY

1.2.1 Pharmacodynamics

A drug is not an intelligent creature, and it does not work as a target-seeking missile. The drug is usually distributed within the body and many drugs are either agonists, activating certain receptors found within the body, or antagonists blocking activation of the receptor. One example of an agonist is morphine, which exerts its effects on opioid receptors that naturally bind endogenous endorphins. When morphine binds to the receptors it has effects similar to the endogenous substance and thereby inhibits pain, increases well-being and also causes side effects such as constipation and nausea. An example of an antagonist is haloperidol, which binds to dopamine D2 receptors. Haloperidol is used for treatment of psychotic disorders and it inhibits the stimulatory effect of dopamine on the D2 type of the dopamine receptors.

For a drug to be effective it needs to reach the place where it exerts its effect. If the concentration is too high the drug will, with rather few exceptions, cause adverse effects either because too much of effect of the drug, or because it binds to other receptors. Some drugs such as tricyclic antidepressants exert, in a concentration dependent manner, an unwanted anticholinergic effect by binding to muscarinic acetylcholine receptors, inhibiting the effect of endogenous acetylcholine. Inhibition of muscarinic receptors causes anticholinergic side effects such as dry mouth, dry eyes, constipation and urinary retention.

The drug concentration at the target site is usually not measurable by simple methods, but it is often assumed to be correlated with the blood concentration of the drug. The aim of drug therapy is, usually, to treat the patient with the lowest effective dose in order to avoid adverse effects.

The target drug concentration is the concentration needed to achieve sufficient effect without intolerable side effects. This is called the therapeutic interval or therapeutic window.

1.2.2 Drug distribution

When a drug enters the body, it is distributed within the body and the pattern is dependent on many factors such as molecular size, lipophilicity of the drug, and ability to be transported by active transporters. Some drugs are found in a high concentration in the blood, whereas other drugs are highly bound to tissues such as body fat.

If the drug is taken as a tablet, it first enters the stomach where the tablet is dissolved (unless it is covered with a layer that resists stomach acidity). The drug is taken up into the blood, usually via the intestinal mucosa either by passive diffusion or by active transport, and distributed into other body tissues.

The body's handling of the drug is called pharmacokinetics and includes absorption, distribution, transport, metabolism and excretion.

1.2.3 Drug transport

Some drugs are transported by active membrane transporters, which may influence their distribution. Transporters can be found at many places such as in the intestines, in the liver, in the kidney, and in the blood-brain barrier. The blood-brain barrier separates brain fluid from the blood and it protects the brain from toxic substances.

One of the most important drug transporters is P-glycoprotein (P-gp). The role of P-gp appears to be to limit body damage due to xenobiotics. P-gp can be found in the intestines where it acts as an efflux pump, carrying already absorbed drugs back into the intestinal lumen, thereby decreasing the net uptake of the drug. P-gp is also found in the blood-brain barrier, where it transports substances from the brain back to the circulation [25]. Examples of P-gp substrates include digoxin [26] and tacrolimus [27]. Some cancer cells are overexpressing P-gp , making them resistant to certain chemotherapeutic agents such as etoposide and vinblastine [28].

Another transporter that has been shown to alter drug pharmacokinetics is the organic anion transporter protein B1B (OATPB1B) which carries drugs into hepatocytes. OATPB1B transports many drugs, and some examples are rifampicin, simvastatin acid, bosentan and caspofungin [29]. Statins exert their effects by inhibiting 3-hydroxy-3-ethylglutaryl-coenzyme A (HMG-CoA) in the liver and decreased OATPB1B transport may cause increased statin concentration, adverse effects, and decreased efficacy [30].

There are also many transporters found in the proximal tubule of the kidney, transporting molecules into or out of the urine. Many drugs are actively excreted into urine. For example, organic cation transporters (OCTs) transport positively charged drugs such as metformin [31] from the blood into the proximal tubule.

1.2.4 Drug metabolism

Although some drugs are excreted unchanged in the urine, most drugs have to be metabolized to more water soluble molecules before being excreted. Metabolism can be divided into phase I and phase II. In phase I, the drug is oxidized, reduced, or

hydrolyzed into, usually, a pharmacologically inactive substance. In phase II, the drugs are conjugated with other more water soluble molecules such as a glucuronide, or an acetyl group. Some substances do not undergo phase I metabolism, and they are only conjugated before excretion. Others are only metabolized by phase I enzymes before excreted. Most of the metabolism occurs in the liver, although other tissues also have some capacity to metabolize drugs.

1.2.4.1 Phase I metabolism

Phase I metabolism is predominately catalyzed by cytochrome P-450 enzymes. Among these, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 are the most important enzymes involved in drug metabolism and will thus be further discussed. For each enzyme examples of substrates, inducers and inhibitors are given.

CYP1A2 is responsible for the metabolism of e.g. clozapine [32], caffeine [33;34], and theophylline [35]. CYP1A2 is also responsible for the metabolism of amines from tobacco smoke and fried food into reactive procarcinogens [36]. Smoking, intake of barbequed food, and broccoli may induce the expression of CYP1A2 [37]. The enzyme is also induced by drugs such as carbamazepine [38], and rifampicin [39]. Examples of inhibitors of CYP1A2 are ciprofloxacin [40] and fluvoxamine [38].

CYP2C9 mainly metabolizes weakly acidic drugs such as warfarin [11], diclofenac [41] and tolbutamide [9]. Rifampicin is an inducer of CYP2C9 [42], and examples of inhibitors are fluconazole [43], fluvastatin [44], and sulfamethoxazole [45].

CYP2C19 metabolizes many drugs to a small extent, but some of the drugs that are extensively metabolized by this enzyme are omeprazole [46], diazepam [47], and citalopram [48]. Example of inducers are rifampicin [49], and St John's wort [50]. Omeprazole [51] and fluvoxamine [52] are inhibitors of this enzyme.

CYP2D6 metabolizes codeine into the active metabolite morphine [53]. Other substrates of CYP2D6 are haloperidol [54], and metoprolol [55]. CYP2D6 appears not to be inducible, although activity is increased in pregnancy [56]. Fluoxetine [57], quindine [58;59] and bupropion [60;61] are all inhibitors of CYP2D6.

CYP3A4 is the cytochrome that is most important for metabolism of drugs and it metabolizes more than 50% of all drugs on the market [62]. CYP3A4 is expressed mainly in the liver, but also to a relevant extent in the gut. Midazolam is used as a probe drug for CYP3A4 activity in drug interaction studies [22;23;63]. Other substrates are e.g. simvastatin [64], quetiapine [65], and sildenafil [66]. CYP3A4 can be induced by enzyme inducing anticonvulsants (carbamazepine [67], phenobarbital [68], phenytoin [69], rifampicin [70], St John's wort [71], and efavirenz [72]. Inhibitors of CYP3A4 usually cause a significant increase in the concentration of substrates, especially those with a low bioavailability. Examples of inhibitors are HIV protease inhibitors [73], azole antifungals [74], erythromycin [75], and clarithromycin [76].

CYP	Substrates	Inducers	Inhibitors
CYP1A2	clozapine theophylline	carbamazepine rifampicin	ciprofloxacin fluvoxamine
CYP2C9	warfarin diclofenac tolbutamide	rifampicin	fluconazole fluvastatin sulfamethoxazole
CYP2C19	omeprazole diazepam citalopram	rifampicin St John's wort	omeprazole fluvoxamine
CYP2D6	codeine haloperidol metoprolol	no known	fluoxetine quinidine bupropion
CYP3A4	midazolam simvastatin quetiapine sildenafil	rifampicin carbamazepine phenytoin phenobarbital St John's wort	ritonavir erythromycin ketoconazole

Table 1. Some examples of substrates, inducers and inhibitors of certain CYPs.

1.2.4.2 Phase II metabolism

The enzymes involved in phase II metabolism are called transferases, and they add chemical groups to drug molecules to make them larger and more water soluble. The enzymes involved are sulfonyltransferases adding a sulfate, UDP-glucuronyltransferases (UGT) adding glucuronic acid, glutathione-S-transferases adding glutathione, N-acetyltransferases adding an acetyl group, and methyltransferases adding a methyl group [1;62].

Many drugs are glucuronidated by UGTs before being excreted. Most glucuronidation occurs in the liver. Glucuronidation may occur by addition of a glucuronic acid molecule directly to the mother substance, or the glucuronide may be added to a metabolite of the mother substance. Most glucuronides are pharmacologically inactive, but there are examples of active molecules such as morphine-6-glucuronide, which is actually more potent than its mother compound [77]. UGTs have been shown to be inducible by drugs such as ritonavir [78] and rifampicin [79]. Example of substrates, inhibitors and inducers of UGTs are presented in table 2. Valproic acid is a known inhibitor of several UGTs, such as UGT1A4, UGT2B7 and UGT2B15 [80]. Glucuronidation is, in general, less investigated than CYP-mediated metabolism. Many drugs are substrates of several UGTs, and there is still much about glucuronidation that is unknown.

It is known that drugs are substrates of other phase II enzymes, but information about interactions involving these enzymes are lacking.

	Substrates	Inducers	Inhibitors
UGT1A1	ezetimibe [81] etoposide [82] SN-38 (active metabolite of irinotecan)[83;84]	flavonoids [85] phenobarbital [86] efavirenz [87]	gemfibrozil [88] atazanavir [89]
UGT1A3	telmisartan [90] lamotrigine[91]		gemfibrozil [92]
UGT1A4	lamotrigine [91] olanzapine[93]	carbamazepine [80]	valproic acid [80] efavirenz [94]
UGT1A6	paracetamol [95]	carbamazepine [92]	
UGT1A9	R-oxazepam [80] etodolac [96] propofol [97]	phenobarbital [97] rifampicin [97]	efavirenz [94]
UGT2B7	epirubicin [98] morphine [99] zidovudine [100]	phenobarbital [92]	valproic acid [101] fluconazole [102]
UGT2B15	lorazepam [103] S-oxazepam [104]	phenobarbital [92]	valproic acid [101]

Table 2. Some examples of substrates, inducers and inhibitors of certain UGTs.

1.2.5 Pharmacogenetics

The effect of drugs can vary greatly from patient to patient, and this can at least partly be explained by genetic differences. These differences may be due to alterations in the gene encoding for the drug target, making the effect of the drug more or less pronounced or even make the drug totally ineffective. One example of this is polymorphisms in the β_2-receptors that have been associated with decreased efficacy in asthma treatment [105]. Another example when pharmacogenetics is important is when treating breast cancer with trastuzumab. For the drug to be effective the tumors have to overexpress HER2 proteins and patients are genotyped before treatment [106].

Alteration in the genes coding for drug metabolizing enzymes and drug transporters, may dramatically alter patients' exposure to drugs. Genetic polymorphisms may result in expression of an enzyme with decreased or increased capacity to metabolize substrates, and for some enzymes it may result in a non-functional enzyme. The prevalence of certain polymorphisms differs greatly between ethnic populations.

Genetic polymorphisms in the gene encoding for P-gp have been found and linked to level of exposure to some HIV drugs, efficacy of certain chemotherapeutics, and effect of some antidepressants [107;108].

CYP2D6 is the most studied enzyme regarding alteration in drug exposure due to genetics. There are more than 100 genetic alterations found within the CYP2D6 gene [109]. The alterations can result in decreased efficacy when metabolizing drugs or, as in the case of CYP2D6, some polymorphisms may lead to a non-functional enzyme. Increased CYP2D6 activity in patients has also been reported, and it has been shown to be caused by gene duplications. The concentration of a CYP2D6 substrate such as

nortriptyline, may vary greatly among individuals receiving similar doses. The exposure to nortriptyline have been shown to be 332% higher in poor metabolizers (no functional allele) and 79% lower in a patient with 13 gene copies, when compared to extensive metabolizers having two functional alleles [110].

CYP2C9 is another polymorphic enzyme with two polymorphisms, *2 and *3, that are relatively common in a Caucausian population (allele frequency *2 11-16%, and *3 7-10%) [111]. CYP2C9 is the enzyme responsible for metabolism of the active S-enantiomer of warfarin and it has been shown that patients with one *2 allele require 20% lower warfarin maintenance doses, patients with one *3 35% less, and in patients with two *3 alleles the maintenance dose is approximately 78% lower [112]. Mutations in the CYP2C9 gene significantly increases the risk for bleeding during the first two weeks of treatment with warfarin [113]. No non-functional polymorphisms have been reported for the CYP2C9 enzyme.

Other cytochrome P-450 enzymes with important polymorphisms are CYP2C19 and CYP3A5 where mutations can lead to non-functional enzymes.

Several polymorphisms have been found in the genes coding for UGTs. UGT1A1 is responsible for glucuronidation of bilirubin and genetic differences are the cause of Gilbert's disease [114]. This disease causes intermittent hyperbilirubinemia. It has been shown that patient with Gilbert's disease are more prone to adverse effects when treated with irinotecan, due to decreased elimination of the active SN-38 metabolite [115]. Otherwise, little information is available regarding the influence of certain UGT mutations on the exposure to drugs. Since there is a great overlap in substrates and many polymorphisms are co-inherited, the effect of certain polymorphisms on glucuronidation is difficult to study [80].

1.2.6 Therapeutic drug monitoring

Therapeutic drug monitoring is used to optimize drug therapy by measuring drug concentration in patients. The method was introduced in the early seventies, and is used for drugs with narrow therapeutic interval such as digoxin [116]. A patient's drug concentration is measured to identify if it is within the therapeutic interval. Today, more than a hundred substances are routinely measured at the clinical pharmacology laboratory at Karolinska University Hospital. Some of the most common analyses are those of aminoglycosides, to limit the risk for oto- and nephrotoxicity, of antipsychotics and antidepressants, to optimize therapy, and of immunosuppressant drugs to prevent organ rejection and decrease the risk for adverse effects.

1.3 DRUG INTERACTIONS

1.3.1 Drug interaction – definition

A drug interaction occurs when the effect of one drug is altered by another drug, food, or herb. The result can be increased effect, adverse effects, reduced effect, or a total lack of effect of the drug which action is altered. Drug interactions can be divided into pharmacodynamic interactions and pharmacokinetic interactions.

1.3.2 Pharmacodynamic interactions

Pharmacodynamic interactions occur when the effect of a drug is altered due to another drug without any alteration in pharmacokinetics. Interactions can be additive when e.g. two drugs are agonists of the same receptor, and concomitant use causes an increased effect and also an increased risk for adverse effects. One example of an additive pharmacodynamic interaction is concomitant use of MAO-inhibitors and serotonin reuptake inhibitors (SSRIs). SSRIs block the reuptake of serotonin in synapses and monoamino oxidase degrades serotonin in the synapses. When both the uptake and degradation of serotonin is inhibited, the synaptic concentration of serotonin increases dramatically and this causes overstimulation of serotonin receptors [117]. The clinical symptoms of serotonin syndrome are tremor, myoclonus, confusion and agitation. In worst case, serotonin syndrome may cause hyperthermia and muscle rigidity which may be fatal [118]. Other combinations of serotonergic drugs may also cause serotonin syndrome [117].

Another example of a pharmacodynamic interaction is the one between SSRIs and non-steroidal antiinflammatory drugs (NSAIDs). Both drug classes increase the risk for gastrointestinal hemorrhage and the risk is increased up to 6-fold when they are co-administered [119].Classical agonist-antagonist interactions are also classified as pharmacodynamic interactions. One example is less effect of beta-stimulants for asthma treatment in patients using unselective beta blockers. Another example is reduced effect of warfarin when patients treated with warfarin ingest large amounts of vitamin K.

1.3.3 Pharmacokinetic interactions

Pharmacokinetic interactions may change the exposure to the drug causing increased effect, adverse effects, or absence of effect. Pharmacokinetic drug interactions may involve absorption, distribution, transport, metabolism, or excretion (renal or fecal) of the drug (see figure 1).

Absorption interactions can occur when e.g. the drug binds to cations. For example when doxycycline is co- administered with magnesium ions, doxycycline binds to magnesium forming a salt that cannot be absorbed. The uptake of doxycycline is decreased significantly, and the combination may lead to lack of antibiotic effect [120]. Absorption interactions can also be due to alteration in gastric pH. One example is the HIV protease inhibitor atazanavir, which needs a low pH to be sufficiently absorbed. If a proton pump inhibitor is given, the exposure to atazanavir decreases by 62-94% [121;122] and this may result in reduced antiviral activity.

Distribution interactions occur mainly due to competitive binding to plasma proteins. This interaction may occur when two drugs that are highly bound to the same plasma protein are co-administered. This type of interaction gives an increase in free fraction of the drugs, which may cause adverse effect if they have narrow therapeutic intervals. One example of such drug is phenytoin and interactions with acetylsalicylic acid [123;124], and valproic acid [125] have been reported. These interactions often lack clinical significance since they usually are transient.

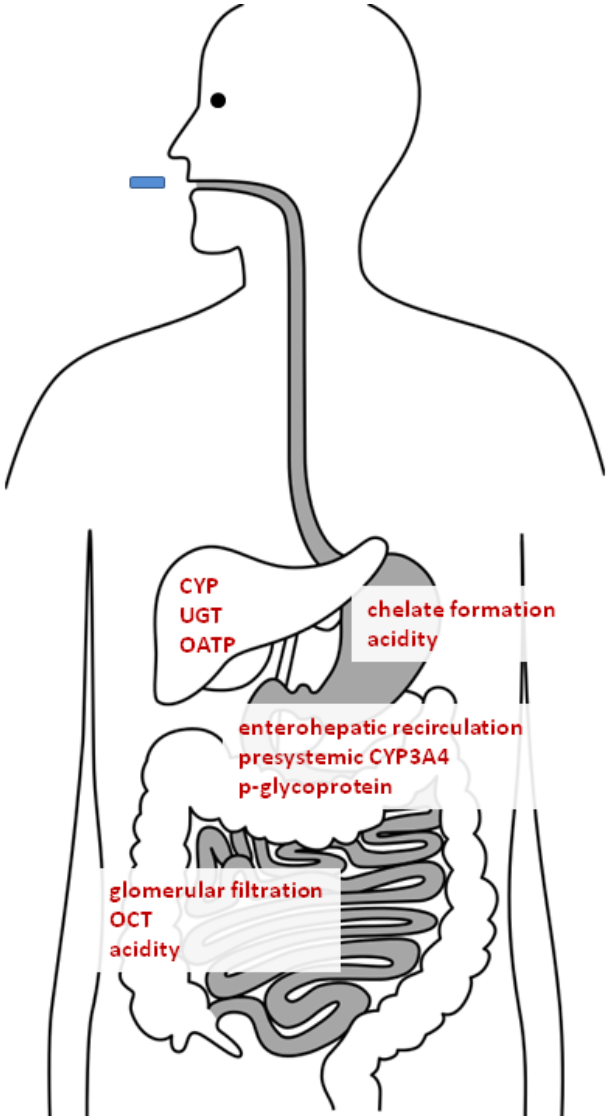

Figure 1. Pharmacokinetic drug-drug interactions can occur at different places within the body. Some occur in the gastrointestinal system, other in the liver or in the kidneys.

Interactions involving transport can increase or decrease the effect of drugs. An example of a drug interaction at transporter level is the interaction between digoxin and verapamil [126], where inhibition of P-gp by verapamil [127] increases the plasma concentration of digoxin. Another example is the interaction between ciclosporin and

atorvastatin [128], where ciclosporin inhibits the transport of atorvastatin by OATP1B1 [129]. This results in decreased uptake of atorvastatin into liver cells, and thereby decreased metabolism and increased statin concentrations.

Metabolic interactions are usually caused by either inhibition or induction of a metabolic pathway. CYP mediated interactions have been well studied and much knowledge is available. One of the most pronounced CYP interactions is between lopinavir/ritonavir and tacrolimus, where the tacrolimus dose may have to be reduced by 99% [130] due to inhibition of CYP3A4. Induction of CYP enzymes can also cause dramatically decreased drug concentration. For example, rifampicin reduces the bioavailiability of nifedipine by 88% [131] and decreases S-warfarin exposure by 75% [132].

Interactions can also occur due to inhibition or induction of UGTs. Valproic acid is a known inhibitor of several UGT enzymes, and clinically relevant interactions occur with UGT substrates such as lamotrigine [133;134] and mycophenolic acid [135]. Induction interactions have been reported between lamotrigine and inducers such as rifampicin [79] and carbamazepine [134]. Much is still unknown regarding drug interactions caused by inhibition or induction of UGTs.

Drug interactions involving urinary excretion can occur when for example one drug changes the pH of urine causing less excretion of the other drug. Changes in renal blood flow can also change the excretion of drugs. NSAIDs can decrease renal blood flow and this may cause increased concentration of lithium [136], which is excreted in unchanged form in urine.

1.3.4 Drug interactions with food or natural remedies

Some drugs may interact with food. Calcium containing products such as milk and yoghurt may, by chelate formation, decrease the uptake of tetracyclines and fluoroquinolones. The uptake of ciprofloxacin may be lowered by approximately 30-40% [137] which may result in therapeutic failure.

Grapefruit juice has been shown to be a potent inhibitor of CYP3A4 [138] and P-gp and ingestion may cause dramatic increases in the concentration of drugs that have low bioavailiability such as nifedipine [139]. The interaction is mostly due to inhibition of intestinal CYP3A4 and P-gp [138]. Other fruit juices may also influence the pharmacokinetics of drugs. Orange juice can decrease bioavailiability of atenolol [140] and pomegranate juice has in a few cases been shown to increase the effect of warfarin [141].

Natural remedies can also cause clinically important drug interactions. St John's wort is a potent inducer of CYPs and concomitant use may cause pronouncedly decreased concentrations of other drugs. Many pregnancies have been reported due to lack of effect of oral contraceptives [142]. Other herbs such as ginkgo biloba [143], and ginseng [144] also interact with drugs.

Smoking is a life style factor that may have great influence on drug therapy. Smoking induces CYP1A2 and e.g. clozapine exposure is about 40% lower in smoking patients [145].

1.3.5 Evaluation of drug interaction studies

Drug interactions can be studied in many ways. In vitro system using human liver microsomes give information about which enzymes that may be involved in the metabolism of a drug. Results from in vitro studies should be used as an indication of interaction but not as evidence of an interaction.

Many drug interaction studies are performed as cross-over studies in healthy volunteers. Results from these studies give valuable information about drug interactions in general. There are, however, some limitations to this kind of studies. The number of study subjects is usually small, and inclusion of a single patient with different genotype or some other reason for altered pharmacokinetics may influence the result. It is also important that the doses used are the same as therapeutic doses, since pharmacokinetics may be different using other doses. The length of drug administration may also be important and steady-state data is often aimed for. If induction is studied the length should, ideally, be long enough to reach maximum induction and a new steady-state.

Drug interactions may be studied using data from TDM databases. Interactions are studied by comparing concentration/dose ratios among exposed versus unexposed patients. When evaluating these studies one should bear in mind that patient data in a TDM material may not be representative for all patients since TDM is often used when problems occur. However, using TDM data may also have benefits since the measurements are made in patients and not in healthy volunteers, thus it could be more representative for the users of the drugs.

1.3.6 Polypharmacy and interactions

The more drugs a patient uses the more likely is the risk of being exposed to drug-drug interactions. When concomitant drugs interacting in several ways are co-administered the net result of an interaction is difficult to assess and it can also differ among patients due to environmental and genetic factors.

For many drugs, metabolism may be dependent on more than one CYP, and if one of the CYPs is inhibited no clinically relevant interaction may be observed, but if the other path also is inhibited the patient might be exposed to a significant interaction. For example, oxycodone is metabolized by both CYP3A4 and CYP2D6. Inhibition of one of the enzymes does not cause a clinically significant change in the effect but inhibition of both enzymes may cause dramatically increased concentration [146], which may cause respiratory depression. Such a case could easily occur for example in a patient treated with fluoxetine, inhibiting CYP2D6 [57], for depression and started on erythromycin, inhibiting CYP3A4 [75], for treatment of a respiratory infection.

1.3.7 Pharmacogenetic differences

Pharmacogenetics may also influence the occurrence of drug interactions. In the case of oxycodone the drug effect is not significantly altered in poor metaboliser of CYP2D6 but if a CYP3A4 inhibitor is co-administered the concentration will increase dramatically [146].

If an inhibitor of CYP2D6 is given to a poor metaboliser, the concentration of a CYP2D6 substrate will not be altered [147], since the patient does not have any CYP2D6 that can be inhibited. The same is true for CYP2C19 and one such example is the interaction between diazepam and omeprazole. Omeprazole increases the concentration of diazepam in extensive metaboliser of CYP2C19 whereas no significant change is observed in poor metabolisers [51].

1.4 DRUG INTERACTIONS – OCCURRENCE AND CLINICAL RELEVANCE

1.4.1 Prevalence of drug interactions

Drug use has increased steadily since more drugs have entered the market and also because the population tends to get older and older. Between 2005 and 2008, the total drug use (defined as number of drugs during 3 months) per patient in Sweden increased by 3.6 % and the total prevalence of polypharmacy (patients with five or more drugs) increased by 8.2%. The number of patients exposed to 10 or more drugs increased by 15.7% [148]. Another, older Swedish study revealed that the number of drugs used by patients 77 years or older had increased from 2.5 to 4.4 between 1992 and 2002, while the prevalence of polypharmacy in this age group increased 3-fold (from 18 to 42%) [149].

The risk for drug interactions increases dramatically by the use of more drugs. Theoretically, the maximal number of potential drug-drug interactions in an individual patient can be described by this formula:

$$\frac{number\ of\ drugs^2 - number\ of\ drugs}{2}$$

For example, a patient using three drugs may in worst case be exposed to three interactions. A patient using five drugs may have ten interactions, and a patient using ten drugs may, at least theoretically, be exposed to 45 drug interactions. Increases in polypharmacy may therefore greatly increase the prevalence of drug-drug interactions. Of course, it is almost impossible that every drug used by a patient on 10 drugs would interact with every other drug but it shows that the potential for interactions is increasing non-linearly. In one study, investigating drug interactions in the emergency department, the risk of a potential drug interaction was 13% among users of two drugs and it was as high as 82% among patients using seven or more drugs [150]. In another study investigating CYP mediated drug interactions among patients on polypharmacy the probability of at least one drug interaction was calculated. The risk was 50% in patients using 5-9 drugs, 81% in those using 10-14 drugs, 92 % in those with 15-19

drugs and 100% in patients using more than 20 drugs [151]. In a Dutch study the prevalence of drug interactions in patients aged 70 or older was increased from 10.5% to 19.2% between the years 1992 and 2005. The prevalence of serious drug interactions (potentially life threatening) almost doubled from 1.5% to 2.9% [152].

Many studies have investigated the prevalence of potential drug interactions based on prescription data and figures ranging from 6 to 89% have been reported [153]. Data from this kind of studies are almost impossible to compare since the definition of potential drug-drug interactions often are is differently classified, and a DDI classified as severe in one database might be classified as of minor importance in another database or is completely missing. The source has great influence on the number of interactions found since some drug interaction databases only includes a small number of drug-drug interactions whereas others may include many more e.g. Swedish Finnish Interaction X-referencing (SFINX) can today identify more than 17 000 drug-drug interactions. In a yet unpublished study based on all dispensed drugs in Sweden during 4 months, the total number of interacting drug combinations according to SFINX were >2 000 000. The prevalence of C and D interactions were (n >900 000), and (n = >90 000) respectively [154]. In the end of 2013 there were around 9.6 million people living in Sweden [155].

Of more interest are studies investigating actual drug-drug interactions that have caused some kind of clinical problem and lead to hospitalization or emergency department visits. In a large review of published studies the overall incidence of drug-drug interaction resulting in emergency department visits was 0.054 %, and 0.57% for hospitalizations. However, in elderly patients drug-drug interactions were assumed to be the cause of 4.8% of admissions [156]. In general the risk of adverse drug interactions leading to hospital admission seems to be low but several studies suggest that it is much more common in elderly patients than in younger. This is in line with the increased number of drugs used by the elderly. They may also be more prone to drug interactions due to for example decreased renal function exposing them to higher drug concentrations. In some patient groups such as HIV-patients, patients using anticonvulsants and patients on chemotherapy the risk for hospitalization is probably higher due to use of interacting drugs with narrow therapeutic intervals.

1.5 CLINICAL DECISION SUPPORT SYSTEMS

In the information age we live in, the problem usually is not to find information but rather to grasp only the most important information. Increasing knowledge about treatment options, new guidelines, new drugs and more specific drug information makes it almost impossible for health care personnel to keep up with and have everything available when needed. To guide prescribers and pharmacists when making decisions on how to handle e.g. patients' drug treatment, clinical decision support systems (CDSSs) have been developed. A CDSS is a system that, optimally, uses patient specific data to give the user case specific advice. CDSS can give users immediate information about e.g. duplicated drug treatment, drug-drug interactions, drug use in pregnancy and overdosing when prescribing. CDSSs are used to decrease errors, increase patient safety, improve health care and save time.

CDSSs are based on knowledge bases providing information. The quality of the knowledge base is one of the factors determining the usefulness and trustworthiness of a CDSS. Information in a knowledge base should be structured in a way that it easily can be integrated into an electronic health care record system or into a dispensing system at the pharmacy. It should be possible to link patient specific data such as e.g. patients complete drug list, age, sex, kidney function through various algorithms to the database. Knowledge bases can also be provided through a website where the patient linkage is missing.

Knowledge bases in CDSSs should, ideally, be evidence based and developed in close collaboration between experts within the area, software developers and potential users of the system.

1.5.1 Drug-drug interaction warning systems

Drug-drug interactions warning systems are commonly used in CDSSs. When used, they warn the prescribers or pharmacists when prescribing/dispensing interacting drugs. For example, when a prescriber initiate treatment with a new drug this drug is checked against all the drugs that the patient is already using and drug-drug interaction information is then presented. In some systems the alerts are intrusive, forcing the user to read them and the system may even require provision of a reason if the user overrides the warning. In other systems warnings are shown in a non-intrusive manner. Color coding may also be used to hint about the seriousness of the warning. Some drug interaction warning systems, such as SFINX [157] and Stockley's Interactions Alert [158], are available both in a web version and integrated into electronic health care records.

Interaction texts should be structured to improve readability and make integration into electronic health care records easier. Background information including references is useful and strengthens the evidence for the specific interaction. This increases the perceived trustworthiness of the source.

Usage of drug-drug interaction warning systems can in some instances decrease prescribing of interacting drugs [159], but studies showing evidence of clinical benefit is lacking [160]. Unfortunately, drug-drug interaction warning systems are often not used optimally. Limitations are mainly due to over-alerting. Many systems give the user too many warnings and/or warnings that are irrelevant for the patient the physician is treating. This makes the user annoyed and less likely to care about the warnings shown. Irrelevant warnings may also occur due to bad implementation e.g. warnings may be given due to old prescriptions that are still stored in the patient's medication list [161].

Not much is known about the dangers of overriding alerts. A Dutch study investigated how often ECG was taken in patients after the prescriber had overridden a warning about risk for QT-prolongation. They found that in 33% of the patients an ECG was taken within a month after initiation of concomitant therapy. Among patients with ECG taken before and after treatment initiation, 31% had an increase in QTc-interval increasing the risk for torsade de pointes [162]. This indicates that overriding of QT warnings may, theoretically, lead to significant QT-prolonging in many patients.

Classification of interaction according to severity is beneficial in increasing alert acceptance among prescribers [163] and preferred by users [164]. The classification system makes it possible to tailor the system better by displaying the warnings in different ways due to severity. This has been shown to decrease the problem with over-alerting. Also the signal to noise ratios are often poor [165] and many of the warnings are overridden by the users. Another feature that users prefer is recommendations on how to handle interactions [166;167]. These recommendations should be clear and as general as possible.

The quality of drug-drug interaction warning systems has been questioned. Comparisons have shown that even among the most severe warnings there coverage varies greatly between different sources [165;168]. This can be due to inclusion criteria for a database (e.g. exclusion of certain pharmacodynamic interaction), but there could also be other reasons such as non-critical inclusion of all interactions mentioned in the product information.

One should always remember that even if an almost perfect drug-drug interaction warning systems gives useful information, the decision on how to handle the specific patient should always be made by the prescriber. There may be cases where serious drug-drug interactions are intended and beneficial or drug treatment is absolutely necessary. The system may also give recommendations that are not useful for each patient since recommendation texts are written for the most common indication of a drug.

2 AIMS

The main aim of this thesis was to design and create a drug-drug interaction database, suitable for integration into clinical decision support systems, to evaluate the user satisfaction with the knowledge base and its effects on prescribing habits with respects to potentially serious drug interactions, and to use previously collected data to find new valuable information regarding specific drug interactions.

The specific aims of the included studies were:

Study I: To develop a drug-drug interactions database especially optimised for inclusion in a clinical decision support system.

Study II: Use data from our therapeutic drug monitoring database to investigate the possible interaction between lamotrigine and quetiapine.

Study III: Use data from the Warfarin genetics study (WARG) to study if the interaction between warfarin and simvastatin is dependent on genetic variations in the metabolism of warfarin.

Study IV: To evaluate how the drug interaction database SFINX is perceived, and to measure the usage among users of the web version.

Study V: To study the influence of integration of SFINX, as a clinical decision support system, on the prevalence of prescription of potentially serious drug-drug interactions.

3 METHODS

3.1 STUDY POPULATIONS

Study II was based on data from the routine therapeutic drug monitoring service database at Clinical Pharmacology at Karolinska University Hospital. The database holds information about all drug measurements since 1991 and is a valuable resource for drug interaction studies. Data were used to identify patients exposed to quetiapine with or without concomitant lamotrigine. Information about drug concentration, dose, sampling time, dosage form used and other concomitant drug was retrieved for all patients included in the study.

In study III, we used data from the WARG study [169], a prospective cohort study with the aim of identifying risk factors for adverse outcome of warfarin therapy. The cohort consisted of 1523 patients. All these patients were genotyped for genes important for warfarin effect such as CYP2C9 and vitamin K epoxide reductase subcomplex 1 (VKORC1). Other medications used were also registered. In study III, we extracted all patients who had used simvastatin and warfarin simultaneously and compared them with all other patients within the cohort.

In study IV, an e-mail invitation to answer a questionnaire about SFINX was sent out to all registered users (n=11763) of the web version of SFINX (available at http://www.janusinfo.se). Among these users most are health care personnel and pharmacists but anyone in Sweden can register as a user and many student, patients and relatives are registered. Since the major aim of the study was to investigate the use of SFINX by prescribers and pharmacist only answers from physicians, midwives, dentists, nurses with prescribing rights and pharmacists were included in the analysis.

In study V, we contacted the head of each primary health care centers (n=26) in the northwestern part of Stockholm County. Some of the centers started using SFINX in February 2007 (SFINX group), integrated into their electronic health record system, and some did not have any electronic drug interaction warning system (control group). Twenty of the primary health care centers agreed to participate in the study. Thereafter we retrieved data from the Swedish Prescribed Drug Register on all prescription from these health care centers for the two time periods September to December 2006 and for the same months 2007. In total we had data on 90 806 prescriptions during 2006 and 91 489 prescriptions in 2007. Among these approximately 19% were in the control group and the rest were in the SFINX group. In the SFINX group we had data from approximately 20 000 patients in each period and in the control group we only had data from around 5000 patients per period. The patients had a median age of 58 in each group with an interquartile range of 40 or 41 to 70 or 71 indicating that the groups were rather similar. The gender distribution was also similar in all groups with 39-40% men.

All studies based on patient data (II, III, and V) were approved by the Regional Ethics Committee.

3.2 SWEDISH PRESCRIBED DRUG REGISTER

The Swedish Prescribed Drug Register is a register of all dispensed drugs in Sweden [170]. It was started in July 2005 and is held by the Swedish National Board of Health and Welfare. The register contains information about drugs prescribed, date of prescription and dispensing, profession and workplace of the prescriber, the age, gender, place of residency and personal number (unique identifier) of the patient. The register does not hold information about drugs given in hospital or drugs purchased over the counter. The use of personal identity numbers in the register is valuable for research since it makes it possible to link this register with other registers such as the register of in-patient care or the register of deliveries.

3.3 STATISTICAL METHODS

For descriptive data median and interquartile ranges were calculated. Proportions were compared using Fishers exact test (study V). T-test was performed to analyze differences in a continuous variable between two groups (study III)

Multiple linear regression was used to analyze effect of different variables on a continuous variable (Study III) and logistic regression was used to analyze the effect on binary variables (study V).

Mann-Whitney U test was used to compare grouped, continuous non-normally distributed data (study II). For paired analyses of continuous non-normally distributed data, and ordinal data, Wilcoxon signed rank test was used (Study II, study IV).

Spearman rank correlation was used to investigate correlation between two non-normal distributed continuous variables and also between two ordinal variables (study II, study IV).

All tests were two sided and $p<0.05$ was considered as statistically significant. All statistical analyses were performed using R [171].

4 RESULTS

The designs are only briefly described and only the main findings are presented in this chapter of the thesis. Further information is available in the published papers and in the manuscript (paper IV).

4.1 STUDY I

4.1.1 Design

This study describes the concept of the SFINX knowledge base. SFINX was built in collaboration between Karolinska Institutet, Stockholm County Council and Turku University. Important steps in building the database were handling of substances, e.g. the development of the mother-child concept for salts, handling of their formulations, classification of interactions, standardization of texts, development of standard operating procedures and the process of text writing and approval.

4.1.2 Results

The result of this work is a database used both in Sweden and Finland. SFINX is incorporated in health record systems in both countries and is also available as a web solution in both countries. At the time of manuscript writing the database consisted of more than 8000 interaction drug pairs and more than 31 000 pharmacists and physicians were using the database. The texts are structured into four parts, consequence, recommendation, mechanism and background. An example of an interaction text found in SFINX is shown in figure 2. All background text have numbered references showing the scientific evidence of the interaction. The consequence and the recommendation texts are translated to Swedish and Finnish and they appear at first when SFINX is used in the portal version and in electronic health care records.

A “read more” link is shown for users who want more information about the interaction. The database considers drug dosage form and thereby the noise due to unnecessary warnings is limited. All interactions are classified from A to D according to their clinical relevance and from 0 to 4 according to the level of documentation.

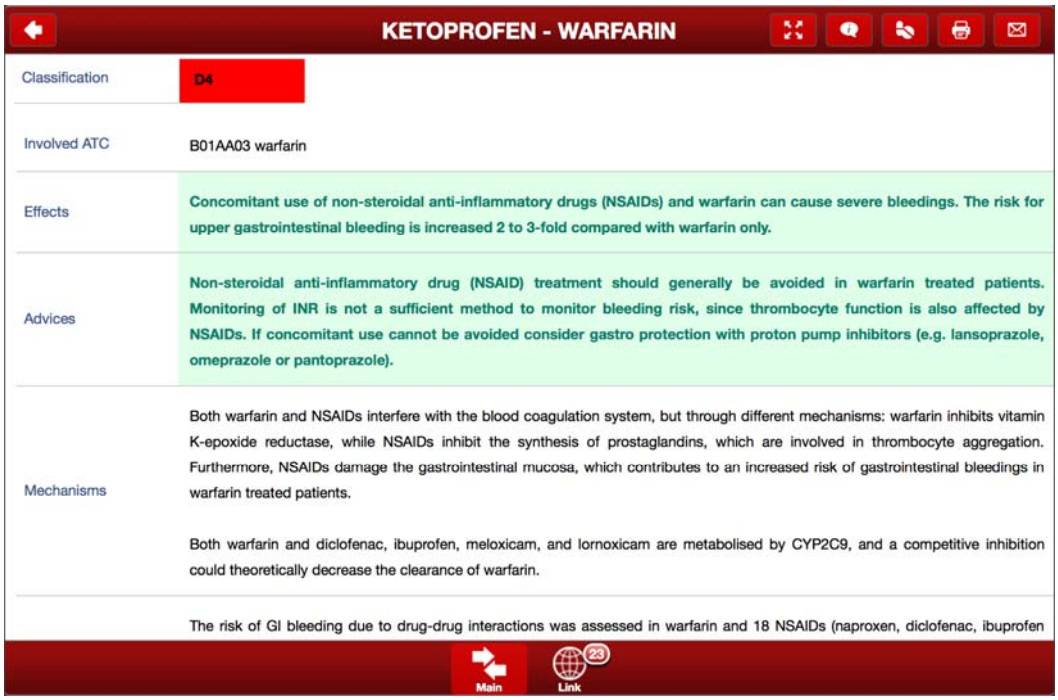

Figure 2. Example of an interaction text in SFINX. The consequence and recommendation texts are translated into Swedish and Finnish.

4.2 STUDY II

4.2.1 Design

Study II was a case-control study investigating the interaction between quetiapine and lamotrigine. All subjects exposed to quetiapine were extracted from the TDM database (n=422). Among these, 22 had received concomitant therapy with quetiapine and lamotrigine. These patients were matched for gender, age and dosage form of quetiapine with 22 patients unexposed to lamotrigine. Concentration/dose (C:D) ratio was compared between patients exposed and unexposed to lamotrigine both in a paired analysis and in an unpaired analysis. The effect of lamotrigine exposure on the quetiapine C:D ratio was also analyzed.

4.2.2 Results

The mean C:D ratio of quetiapine was found to be significantly lower in subjects co-treated with lamotrigine (0.71, 95% C.I. 0.46-0.97) compared to the C:D ratio in their corresponding controls (1.64, 95% C.I. 1.00-2.28) p=0.013. Figure 3 shows the difference in C:D ratio between cases and controls. Quetiapine concentration (dose-corrected) was 58% lower in patients co-treated with quetiapine and lamotrigine. We did not find any correlation between lamotrigine exposure and quetiapine C:D ratio.

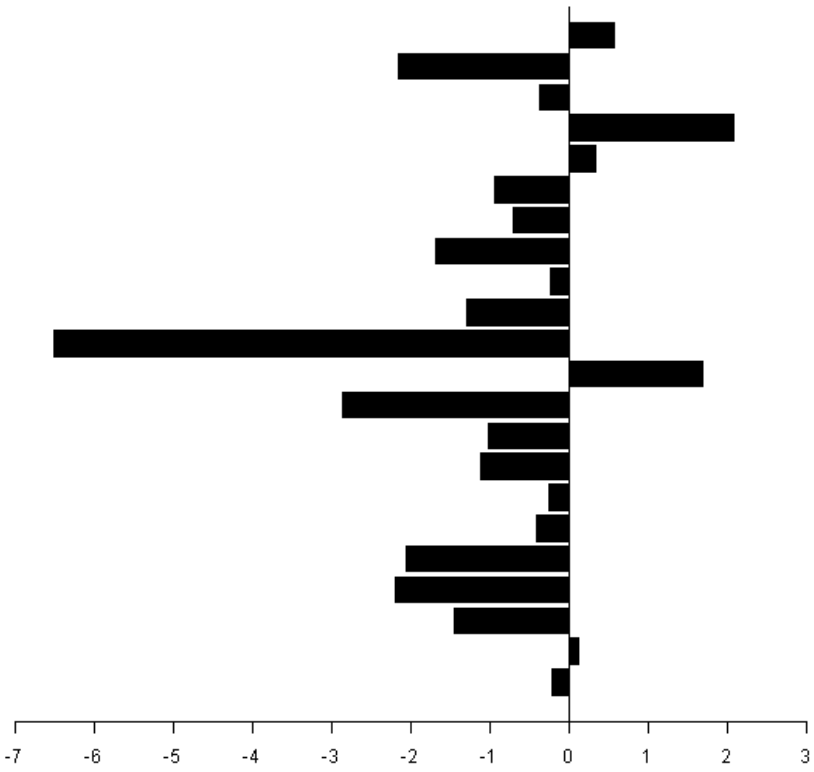

Figure 3. Difference in quetiapine C/D ratio (µmol/L)/(mg/d) between cases (co-treated with lamotrigine and quetiapine) and matched controls (unexposed to lamotrigine). Each bar illustrates the difference between the C/D ratio of an individual case and its corresponding matched control. Negative values indicate a lower C/D ratio in the lamotrigine-exposed individual.

4.3 STUDY III

4.3.1 Design

Data from the WARG study was used to analyze if polymorphisms in the CYP2C9 gene influence the magnitude of the interaction between warfarin and simvastatin. Patients who had received warfarin for at least 28 days, not using other drugs that alters INR and successfully genotyped for CYP2C9 were included in the study. To be included in the simvastatin group the patients should have received warfarin and simvastatin concomitantly for at least 28 days. The median weekly warfarin dose during 90 days of therapy (starting 15 days after initiation of treatment) was calculated for each patient. If the patient had not received warfarin for 90 days all days on warfarin was included. In the simvastatin group the median weekly dose was calculated from day 15 on concomitant therapy. In the primary analysis we compared the warfarin dose in patients using simvastatin with patient not using simvastatin. To analyze the impact of genotype on the interaction we did a multiple regression including an interaction between genotype and simvastatin use.

4.3.2 Results

The number of patients who met the inclusion criteria was 1132 where 143 were included in the simvastatin group and the remaining 989 were included in the control group. In all patients, usage of simvastatin was associated with an 8% lower weekly warfarin dose (p=0.045). In patients carrying at least one CYP2C9*3 allele the warfarin maintenance does was significantly lower, -21.4%, if treated with simvastatin. When using multiple regression to adjust for other factors we found no significant effect of simvastatin on the warfarin dose requirement except for in patients with CYP2C9*3 alleles. According to the model a patient with one *3 allele should have a 25% lower dose when co-treated with simvastatin and a patient with two *3 alleles should have their dose decreased by 43%. Results from multiple regression are presented in table 3.

	Beta	Effect on warfarin dose	p-value
Age	-0.012 (-0.013 to -0.010)	- 1.2 % (-1.33 to -1.03)	< 0.0001
Male sex	0.103 (0.059 to 0.146)	10.8 % (6.08 to 15.72)	< 0.0001
Simvastatin	0.018 (-0.056 to 0.092)	1.8 % (-9.64 to 5.41)	ns
No. of CYP2C9*2 alleles	-0.203 (-0.252 to -0.153)	-18.3 % (-22.28 to -14.19)	< 0.0001
No. of CYP2C9*3 alleles	-0.384 (-0.445 to -0.323)	-31.9 % (- 35.91 to -27.62)	< 0.0001
Interaction Simvastatin × *2	-0.032 (-0.161 to -0.096)	-3.2 % (-14.85 to 10.13)	ns
Interaction Simvastatin × *3	-0.281 (-0.447 to -0.115)	-24.5 % (-36.08 to -10.86)	0.0009

Table 3. Results from multiple regression.

4.4 STUDY IV

4.4.1 Design

Study IV presents the results from a questionnaire sent out to users of the web version of the SFINX database. The questionnaire was designed to receive answers on when and how SFINX is used and also how it is perceived by the users. The questionnaire was sent out to all registered users (n=11 763).

4.4.2 Results

Answers from 1389 prescribers and 464 pharmacists were included in the study. The database was stated to be used weekly or more often by 45% of the prescribers and 51% of the pharmacists. The prescribers reported using the database when meeting patients (60%) or directly before/after (60%). Pharmacists mostly used the database when dispensing drugs to patients (figure 3). Prescribers also reported using the database for drug utilization reviews and education.

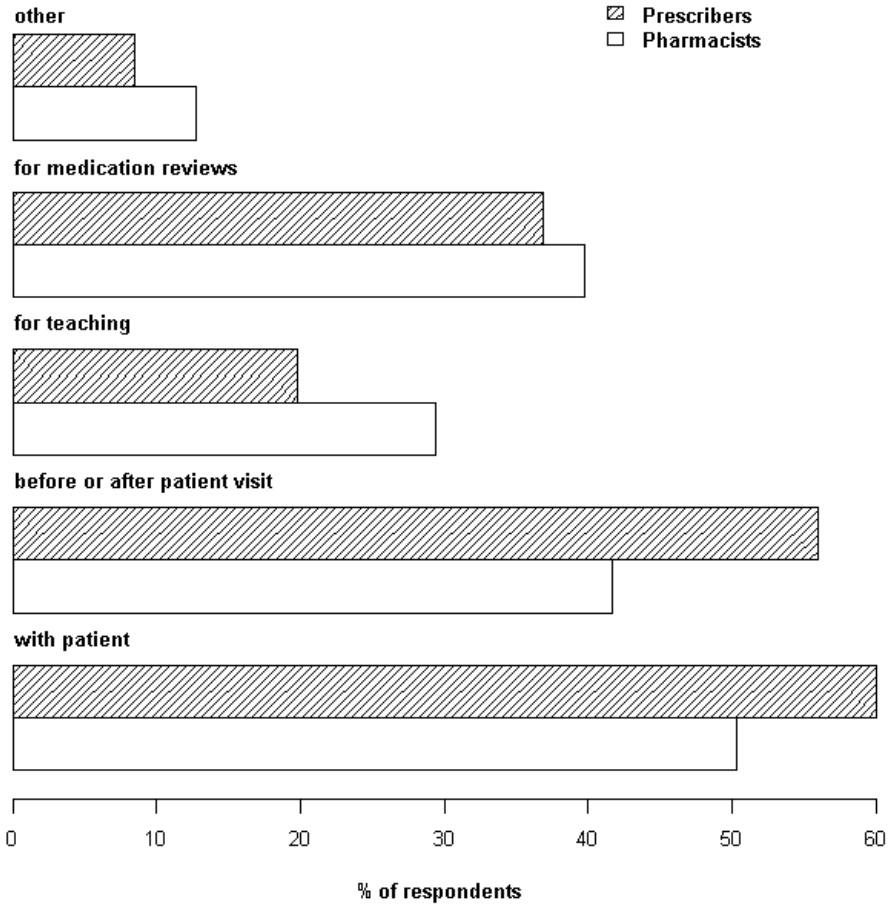

Figure 3. In which situation do prescribers/pharmacists use the database?

Changes in prescribing were reported to occur sometimes or more often by 74% of the prescribers. Among the most common changes, due to the use of SFINX, was changing the drug and informing the patient. Among pharmacists, 93% reported changing their handling of the patient and the most common action was to contact the prescriber followed by informing the patient. Twenty percent of prescribers and twenty five percent of pharmacists reported that the information provided by SFINX was irrelevant sometimes or more often.

4.5 STUDY V

4.5.1 Design

The number of potential drug-drug interactions before and after implementation of SFINX into and electronic health record system was investigated in a controlled study. Primary health care centers in the northwestern part of Stockholm were included in the study. Data from a 4 month period before implementation and for the same months the year of implementation were compared. A control group not using SFINX was also included in the study. Data was retrieved from the Swedish Prescribed Drug Register.

4.5.2 Results

In total, twenty health care centers participated in the study, fifteen in the SFINX group and five in the control group. Data on approximately 91 000 prescriptions to 25 000 patients was analyzed per period. We found a significant, 17% decrease in the number of potential drug interactions in the group using SFINX while the change in the control group was non-significant. Logistic regression did not show any significant difference between the two groups. The study did have very low power to show any difference since the control group was smaller than aimed for.

5 DISCUSSION

Detecting and managing interactions between drugs is a clinical challenge. Drug-drug interaction warning systems play a major role in aiding physicians, other prescribers, and pharmacists when prescribing or dispensing drugs to patients. Despite the fact that warning systems are being introduced at most health care facilities, many patients are still prescribed potentially harmful drug combinations. The reasons behind this phenomenon are not known. However, possible explanations are incomplete patient drug lists in an electronic health record system, underuse due to bad integration of the system and over-alerting. In many cases, drug-drug interactions do not have any clinical consequences at all, and the combination may be well tolerated. In some cases, the specific combination may intentionally be prescribed to a specific patient for beneficial effect, despite being judged as a combination that usually should be avoided. One such example is co-prescription of verapamil and metoprolol, a combination that can cause atrioventricular block, bradycardia and hypotension [172]. In general, this interaction should be avoided, but it may in some cases be beneficial. Other interactions do have clinical impact and may cause serious adverse effects or result in therapeutic failure.

The main scope of this thesis was to design a knowledge database, and to measure user satisfaction, and impact on prescribing when the database is used and integrated into an electronic health record system. When designing the database SFINX, we wanted to create a knowledge database useful in the clinical situation. Alerts should, as far as possible, aid drug prescribing without annoying the users or give unnecessary warnings. The main tools to improve the signal to noise ratio were to classify drug interactions and to give warnings based on administration routes for the drugs. To make it easy to use when meeting patients, we aimed at writing short, stringent texts describing the clinical consequence of the interaction and to give clinically useful recommendations. Strategies used are described and discussed below.

5.1 STRATEGIES FOR USEFUL DRUG-DRUG KNOWLEDGE BASES

5.1.1 Classification of drug-drug interactions

Classifying of drug-drug interactions according to clinical relevance has been shown to be an efficient way to increase acceptance of drug-drug interaction warnings [163;173]. The classification system from a previous Swedish drug-drug interaction warning system [20] was well accepted and known by the Swedish users. This classification system was only slightly modified to be able to show where interactions were extrapolated to similar drugs in the SFINX database. In SFINX, the interactions are graded from A to D according to clinical relevance and from 0 to 4 according to level of documentation.

The grading of drug-drug interactions makes it possible to differentiate the type of warnings when SFINX is used in a CDSS. Our recommendation is to use different color coding for the different interactions where D should be red, C yellow and B and A white. Color coding may be one approach to inform the prescriber about the

existence of a certain type of interaction [164]. Another option would be to show all C- and D-interactions in an intrusive manner, whereas B and A could be shown in the prescribing system without any interruption.

One problem with color coding may be that prescribers only recognizes the colored interactions and totally disregards the other interactions. Some prescribers may even only react on red warnings, which might be dangerous, since many C interactions are as severe as D interactions if no action is taken. In study IV, 17% of the prescribers reported reading only the texts for C and D interactions, whereas 4% reported reading only the texts for D-interactions.

B-interactions are those where the 'clinical outcome of the interaction is uncertain and/or may vary'. In this group there are interactions where exposures are somewhat altered in the whole population, but where the clinical consequence is unknown. We also have B-classified interactions that are based on one or a few case reports and where we have found no other evidence for the interaction. Some of the interactions that are B-classified occur only in some patients but not in others, maybe due to genetic factors such as e.g. the dependence of the CYP2C9*3 allele as found in study III. In some cases, a B-interaction may be as severe as a D-interaction and hiding this information may result in unwanted unawareness. The optimal way, in my opinion, is to have the B-interactions in the system but shown in a non-alarming way. If the physician sees a patient describing side effects, this information can be read and maybe the interaction is the cause of adverse effects in this patient. It is important to know that the database can be used not only for screening of interactions, but it is also a valuable tool to find a reason for an occurring drug problem.

5.1.2 Inclusion criteria

The number of interactions included in the knowledge base will influence the number of warnings given. If all possible interactions, both pharmacokinetic and pharmacodynamic are included, the number of interactions in the database will be very large. In SFINX, we have decided to mainly include pharmacokinetic interactions, but we are also including pharmacodynamic interactions that are not obvious due to the action of the drugs. For example, we do not warn for concomitant use of beta stimulants and beta blockers, since that interaction is expected if you know about how the drugs work. An example of a pharmacodynamic interaction that is included is the interaction between NSAIDs and SSRIs, causing an increased risk for hemorrhage. Not everybody knows that SSRIs increase the risk for bleeding and the risk is also more than additive, hence this interaction is included in SFINX. Of course, there are many prescribers and pharmacists that would like to be warned even about the obvious pharmacodynamic interactions, but we assume that by adding them the signal to noise ratio would be unfavorable, increasing the risk for alert fatigue.

To make it possible for prescribers to evaluate the risk for some pharmacodynamic interactions we have developed Pharmacological Risk Assessment Online (Pharao) as a new tool. In Pharao we have graded all substances in SFINX according to their risk for causing anticholinergic side effects, hemorrhage, serotonin syndrome, QT prolongation, seizures, constipation, sedation, orthostatic hypotension and renal

toxicity. The substances are graded from 0 to 3 and we have made algorithms to calculate if the risk is mild, moderate or severe for each of the properties. A sum is calculated for each property, and the user receives a color coded warning according to the risk level. We do want Pharao to be an on-demand system, since mandatory use during prescribing would probably rapidly result in alert fatigue.

5.1.3 Substances and dosage forms

In the previous drug-drug interaction warning system used in Sweden, a lot of interactions were group interactions, according to ATC-codes. This caused some unintentional warnings, for example glucosamine was classified as a NSAID, although glucosamine does not have any similarities with NSAIDs. The same problem has been reported for other drug-drug interaction warning systems [165]. To prevent this, all interaction texts in SFINX are written at substance level, although there is a possibility to share texts between several interacting pairs. The sharing feature diminishes unintentional differences between texts.

Some drug-drug interaction warning systems do warn incorrectly for drug interactions with topical drugs that are not absorbed [165]. Irrelevant warnings may also be given for drugs administered parenterally if the drug interacts only when given orally, as in the case of chelate formation. This makes the system less specific and causes erroneous warnings, annoying the users. A feature to reduce this type of errors was introduced in SFINX by taking route of administration into account when classifying interactions. Any of these routes can be added to an interaction: enteral, parenteral, enteral oral, enteral non-oral and topical, to increase the specificity for of the warnings. One example of a substance where the dosage form is important is midazolam, where the interaction with CYP3A4 inhibitors is much more pronounced if given orally compared to parenterally [174]. In SFINX the interaction between oral midazolam and protease inhibitors is D-classified whereas if given parenteral it is classified as C. These classification options prevent unnecessary warnings especially when drugs are administered topically.

5.1.4 Recommendations

Lack of management advice is common in drug-drug interaction warning systems and recommendations is a feature that users demand [165]. In a survey in the United States, 74% of prescribers and 82% of pharmacists stated that they wanted management alternatives when given drug-drug interaction warnings [167]. To facilitate the handling of interactions, recommendations are given for all interactions in the SFINX database. Recommendations can be that the patient should be carefully monitored for adverse effects, that the drug concentration should be measured or another alternative drug can be used. The recommendations are aimed at being as specific as possible, but in many cases this is difficult since there are no better alternative drugs available, or drug concentrations are not possible to measure. Even indications of the drugs involved vary, and may alter the recommendation texts. The evidence behind the recommendations is varying, some are based on results from clinical trials while others are based on known pharmacological substance properties. Often, both actions to handle the interaction and alternative drugs are given. Unfortunately, we do not know to what extent SFINX users

adhere to the recommendations or if they find them useful enough. In study IV it would have been of value to add a question about the content and usefulness of the recommendations, but unfortunately we did not do this. Another way to study the adherence would be to follow up some specific recommendations within the patient medical journal e.g. if drug levels were measured, doses decreased or increased or if the given alternative drug was chosen. The most common answer, in study IV, on the question about what actions were taken due to information from SFINX was to change the choice of drug (74%). We do not know if they change to alternatives given in the recommendation texts or if they only change because there is a warning. This would require further investigations including follow-up on drug treatment after using drug-drug interaction warning systems.

5.1.5 Implementation

Another important, but often neglected, step for optimizing drug-drug interaction warnings is the implementation of the knowledge base into electronic health record systems. The user interface is really important and it does not matter how consummate the database is if it is not presented in an optimal way to the users. It is also important that the users feel involved in the implementation for the process to succeed [175]. In study V, which yet is the only available study of effects of SFINX on prescription of interactions, SFINX was introduced in health care centers using Swedestar (an electronic health record system). The health care centers were contacted and asked about if they wanted education on the new features of the system, but only four out of fifteen centers had received this information. In the other health care centers the users had only received a pamphlet about the system. Also when SFINX was introduced into the electronic health care records system, Take Care, used at Karolinska university hospital, information about the system did not reach the prescribers sufficiently. The system is non-intrusive and many users may not have noticed the warnings at all.

Unfortunately, the providers of knowledge bases are, most of the times, not involved when the system is integrated into the electronic health records. This may result in inappropriate displaying of warnings, underuse and even false integrations.

Also, when integrating the CDSSs it is of importance to find out when in the prescribing process the prescribers wants the warnings. If the warning is given to late or has a bad timing the physician will have difficulties in using the given warning [176].

5.1.6 Preventing alert fatigue and overriding

Since alert fatigue and overriding is common for drug-drug interaction warnings, it is important to try to minimize these problems. All the above mentioned strategies are attempts to reduce irrelevant alerts and increase alert acceptance. Several studies have shown that drug alerts are often overridden due to reasons such as that the user finds the warnings unnecessary, the medication list is not up-dated causing excessive warnings and warnings are shown repeatedly [177;178].

There are yet not studies investigating the override rates for the warnings given by SFINX. In study IV, one of the questions was how often the respondents find the information irrelevant. On that question 20% of prescribers and 25% of pharmacists

answered sometimes or more often. Since this questionnaire was answered by users of the web version, the figure can be expected to be a bit higher if studying this among users of SFINX integrated into the prescribing systems.

5.1.7 Evaluation

Every knowledge base should be evaluated for quality assurance and further development. Evaluation can be done in several ways. By studying logging of usage one can look at how it is use, what texts are read etc. That is valuable information about the usage. Other ways are to do more qualitative research including questionnaires and interviews. Effects of use of knowledge bases on prescriptions and patient outcome are also important to study and discussed in 5.2.2 below.

In study IV we attempted to evaluate how the web version of SFINX is used and how the users perceive the application and the information provided. No other formal studies issuing this question have been performed yet, despite SFINX being widely used in Sweden and Finland. The answers on the questionnaire gave us much information about how and when the database is used. We learned more about how the users perceive the database. In the questionnaire many users stated that they wanted information about herb-drug interactions and some were later introduced into SFINX. Unfortunately, this feature cannot be sufficiently used in the integrated versions since herbal drugs are usually not prescribed through electronic health record systems. However, in the web version one can easily search for herb-drug interactions.

5.2 EPIDEMIOLOGY OF DRUG-DRUG INTERACTIONS

5.2.1 Measuring drug-drug interactions

There are difficulties in measuring the exposure to possible drug-drug interactions. In study V, we have used all dispensed drugs during a four-month period to estimate the exposure to drugs and their interactions. In Sweden, drugs are usually dispensed for a three-month period. It has been shown that by looking at dispensed drugs during a four-month period you are more likely to cover drugs used for chronic disorders [179], since some patients take out their drug when only a few tablets are left in the package, which might often be more than 90 days after the first purchase. However, by classifying all drugs dispensed to a patient during a four-month period, it is likely that we will slightly overestimate the number of drug interactions. By using the Swedish Prescribed Drug Register, we can only identify drugs that the patient has been prescribed and purchased at the pharmacy. In our opinion, this method gives a more correct measurement of drug use in the patient compared to looking at prescription data in the electronic health records. Depending on what you want to measure you should choose the most appropriate method. If you want to measure how many interacting drugs the physicians actually prescribe it would be better to look at prescriptions, but if we want to look at a more true exposure it is better to use the Prescribed Drug Register. Another reason for using the Prescribed Drug Register is that data on all drugs dispensed is available whereas data on prescriptions is today not as easily available for research.

In our study, we do not have any information about drugs that patients might have purchased over the counter. Additionally, we do not know if the physicians have done anything to prevent the interactions. For many of the interactions found, one of the easiest ways to avoid them is to take a temporary brake with one of the interacting drugs (such as iron or calcium) or to take them several hours apart. Such an action cannot be identified using register data, especially when drug dosing regimens cannot be interpreted. Also, we probably overestimate the prevalence of interactions since some of the interacting pairs have not at all been taken at the same time during the four months period. For example, a patient may have used erythromycin for one week in the beginning of the four month period and then was prescribed a calcium channel blocker several weeks later. By using our method, this will still be classified as an interaction.

The number of patients exposed to potentially serious drug-drug interactions in study V was lower (1.5%) than previously reported (2.9%) in Sweden [180]. Our study is only based on data on all prescriptions from one health care center and does not include the drugs that the patients have been prescribed elsewhere. We have also excluded patients using multiple drug dose dispensing. It has been shown that patients using multiple drug dose dispensing are more likely to be exposed to drug interactions [181].

5.2.2 Studying clinical effects of drug-drug interaction warnings

It is generally assumed that the prevalence of drug-drug interactions will decrease if warnings are given to prescribers. Many studies have investigated the effect but with diverging results. The prevalence of interactions is assumed to be a proxy for the prevalence of clinically consequences due to drug-drug interactions. There are not enough studies published yet to show if warnings actually decreases hospitalizations etc. [160].

In study V, we looked at the influence of integration of SFINX on the prevalence of potentially serious drug-drug interactions and we found a significant 17% decrease. One can speculate if a 17% decrease does have any clinical consequences at all. For many of the D interactions we cannot know if the patient has been exposed or not since it cannot be observed by looking at dispensing data. Examples are all the chelate formation interactions where the prescribers may have informed the patient about how to avoid the interaction. Taking that into account the number of prevented drug-drug interactions could be much higher, but we do not have any information about that.

Today, when much health care money is spent on clinical decision support systems, there is an urgent need for studies on the clinical impact of these systems. Unfortunately, they are not easily performed and not even asked for by the counties paying for the decision support systems. When doing this kind of studies the benefits should be weighed against the time use of the system consumes.

5.2.3 Common drug-drug interactions

In study V, we found that the most common potentially serious drug-drug interactions were those resulting in chelate formation between antibiotics and metal ions or calcium. We do not know if the prescribers have taken any action to prevent these interactions, e.g. advised the patient to separate drug intake by several hours or skipping the

metal/calcium therapy during antibiotic treatment. Co-prescription of potassium and potassium sparing diuretics was also common. In this case co-treatment may be justified if the potassium levels are monitored closely but otherwise the interaction should be avoided. Another common group of interactions are those between opiates that need to be metabolized by CYP2D6 to become active (codeine, tramadol, ethylmorphine) and inhibitors of CYP2D6 (fluoxetine, paroxetine, duloxetine, terbinafine, bupropion). These interactions causes lack of effect and may be less easy to identify than serious interactions that causes side effects. Among the common interactions in study V, were also interactions between calcium channel blockers (felodipine, nifedipine) and enzyme inducers (carbamazepine, phenytoin). These interactions will also cause loss of the blood pressure lowering effect of the calcium channel blockers.

Actions to avoid drug interactions resulting in decreased effect seem to be less than for interactions resulting in adverse effects. It has been shown that physicians are more likely to prescribe CYP2D6 inhibitors together with prodrugs such as codeine and tamoxifen than prescribing CYP2D6 inhibitors and substrates [182]. Such interactions could probably be reduced by using a warning system. Increased knowledge about them could also increase the awareness about them. Many of those interactions did decrease in study V and maybe the prescribers learned about this kind of interactions from the database.

5.3 SFINX – HAVE WE REACHED OUR GOAL?

We aimed to create a knowledge base of drug-drug interactions that should be suitable for integration into electronic health records, clinically useful and not causing unnecessary warnings.

First of all we have created a knowledge base, SFINX, and it is integrated into electronic health care records in Sweden, Finland and Italy. Today, the knowledge base contains over 17 000 drug-drug interaction warnings and it is updated quarterly. Based on the results from study IV, we can conclude that SFINX is used when prescribers and pharmacists meet their patients. Users report that the information does have impact on their prescribing/dispensing. Of course, the respondents are a selected group of SFINX users and we do not know how the system is used and perceived among users of the electronic health record integrated version of SFINX.

The results from study IV can be seen as an indication that we have reached our goal, although more information both of the clinical usefulness and the frequency of unnecessary warnings is needed to confirm this. A further goal that could be set is that SFINX should decrease adverse outcomes due to drug-drug interactions. It is our hope that it does but this would need to be confirmed in a large randomized controlled trial.

5.4 FURTHER REDUCTION OF IRRELEVANT WARNINGS

As shown in study III, some drug-drug interactions may only occur in genetically predisposed patients. Many of these interactions may in SFINX be classified as B-

interactions since they are not that common and may only occur in some patients. One way to further improve drug-drug interaction warning systems could be to warn specifically if a patient has, for example, a genotype predisposing them for a given interaction. For such a system to work we need to have much more knowledge in the area, otherwise it would be difficult to give clear recommendations on how to handle the interactions within these relatively uncommon patient groups. Also, the electronic health record system would need to store the information, e.g. genotype needed to specify the alert. One should also bear in mind that for many drugs there are wide spread differences in exposure that cannot be explained by any, yet known, genetic factor. In our warfarin dosage model in study III we could only explain around 62% of the variation in warfarin dosage when including age, gender, use of simvastatin and mutations in CYP2C9 in the analysis. Other factors that could be included to produce more specific warnings are e.g. kidney function and liver function.

Another way, not used today, would be to adjust warnings according to the patients prescribed dose. Such a limit could be set for example for statins where it has been shown that some interactions are probably irrelevant if statins are given in low doses [183].

5.5 SOURCES FOR STUDIES OF DRUG-DRUG INTERACTIONS

Today the regulatory authorities demand drug interaction studies to be performed before a new drug is approved. This gives information about the general drug interaction properties of these drugs. For older drugs much information is missing and drug companies do not have any economic interest in performing these studies. To find indications of interactions the optimal way is to use already collected data. In study II, we used the therapeutic drug monitoring database to investigate the interaction between lamotrigine and quetiapine. Data from therapeutic drug monitoring is useful for performing drug interaction studies and the drugs analyzed are often those with a narrow therapeutic interval where drug-drug interactions may be more likely to have clinical impact. Another way to identify, still unknown, interactions is using data mining in pharmacovigilance databases [184]. It has also been shown that drug interactions can be found based on data mining from searches in Google, Bing and Yahoo! [185]. In a study, not included in this thesis, we have also shown that drug interactions with warfarin actually can be identified by analyzing dispensing data from the Swedish Prescribed Drug Register [186]. Analyzing of data on diagnoses and drugs used could also be extracted from electronic health records and used for analysis of drug-drug interactions. Linking data from in-patient register with data on prescription is another option to find drug interactions. Table 3 gives a short summary of examples of sources to find drug-drug interactions.

Findings based on above mentioned database investigations should always only be considered as indications of a drug-drug interaction and not as a proof. But they might be helpful to find which drug-drug interaction studies that should performed.

Source	Examples
Pharmacovigilance databases	Swedis EMA database Vigibase
Routine data from health care	TDM databases Electronic health records
Search engine data	Google etc.
Health registers	Prescribed Drug Register In-patient Register Health care quality registers

Table 3. Example of sources to indentify new drug-drug interactions.

5.6 INTERACTIONS INVOLVING GLUCURONIDATION OF QUETIAPINE

In study II, we show that co-treatment with lamotrigine decreases the concentration of quetiapine. The findings in this study should be used with caution since we only had data from 22 exposed patients. The effect is, however, larger than that previously reported by Castberg et al [187] and could have clinical impact. The combination of lamotrigine and quetiapine is commonly used among patients suffering from bipolar disorder. When they are used together they could theoretically have a synergistic effect making them work well enough despite the lowered concentration of quetiapine. The situation could be another in a patient using lamotrigine for epilepsy and quetiapine for treatment of schizophrenia. In that case addition of lamotrigine to ongoing quetiapine treatment could possibly result in worsening of the psychiatric disease.

The results from this study supports the theory that glucuronidation may be important for the elimination of quetiapine, and that drugs inducing or inhibiting glucuronidation may influence the pharmacokinetics of quetiapine. Since most inducers of UGTs are also inducers of CYP3A4 it is difficult to find out which induction that is causing changes in the pharmacokinetics but this could probably be done by analyzing all metabolites. Sparse data describe an increased concentration of quetiapine in patients using valproic acid [188] and this also supports the evidence of glucuronidation as an important pathway for quetiapine metabolism.

Of interest is also the inducing effect of lamotrigine, which may result in other important drug interactions. For example, somewhat lowered levonorgestrel concentration has been reported in patients treated with lamotrigine [189], and this could possibly be due to increased glucuronidation. Decreased clonazepam concentration has also been reported [190], strengthening the assumption that lamotrigine is an inducer of at least some UGTs.

5.7 INHIBITION OF CYP2C9*3 BY SIMVASTATIN

In study III we show that the interaction between simvastatin and warfarin is more pronounced in patients with the CYP2C9*3 allele. The results from the multiple regression analysis indicate that the interaction may even be present only in patients carrying the *3 allele. We speculate that this may be due to selective inhibition, either by simvastatin acid or simvastatin lactone, of the CYP2C9*3 enzyme, but this still needs to be proven. It is already known that the pharmacokinetics of different CYP2C9 substrates is altered differently by polymorphisms in the gene encoding for CYP2C9. The clearance of S-warfarin is reduced by 48% in patients with the CYP2C9*1/*3 genotype, whereas the clearance of diclofenac is not significantly altered [191]. It has also been speculated that fluconazole, a potent CYP2C9 inhibitor, may not at all inhibit CYP2C9*3 [192].

Due to a response letter to our publication [193], we reanalyzed data from study III. In the new analysis we included information about mutations in the VKORC1 gene encoding for warfarin's target molecule. In this analysis there was still a significant effect of simvastatin use in patients with the CYP2C9*3 allele.

Selective inhibition of CYPs due to genetic polymorphisms is poorly investigated. For warfarin there are many single case reports of pronounced interactions whereas no interaction can be observed in clinical trials. These interactions could, theoretically, in some cases be due to selective inhibition of certain variants of the CYP2C9 enzyme.

5.8 OPTIMIZING DRUG-DRUG INTERACTION WARNINGS

The optimal drug-drug interaction warning system should be flexible and easily individualized. All warnings should be accessible, although only those that are deemed clinically relevant should be shown. The warnings should be shown at the optimal time when prescribing e.g. as soon as the physician has chosen the drug and decided the dose. The user should be able to adjust the level of warnings shown and it should be possible to switch off warnings. The possibility to switch off warnings should be available both for a specific user but it should also be possible avoid certain warnings for a specific patient. Ideally, the system should also be able to customize warnings depending on more sophisticated patient characteristics. For example interactions occurring only in persons with certain genotypes should only be shown in patients not genotyped or known to have the predisposing genotype. The system could as well be linked to laboratory parameters and e.g. warn when patient using potassium and potassium sparing diuretics have high potassium levels or when potassium has not been measured within a certain time. This approach has already been tested. In a study from 1994 warnings for interactions were generated if laboratory values were not measured within a few days after concomitant therapy had been initiated or if measurements taken were above certain limits. For example, in patients using digoxin and quinidine the digoxin concentration should be measured within 5 days and it should then be below a certain value not to generate any warning [194].

In cases where measuring of drug concentration is advisable it could have benefit if the user could easily order the concentration measurement when prescribing the potential interacting drugs. Warnings should also ideally be shown when one drug is withdrawn and if that drug is an inducer the warning should also inform the user that it can take some weeks until a new steady-state is reached. Table 4 shows some factors that could possibly be useful for targeting drug-drug interaction alerts.

Factor	Explanation
Age	Some adverse effects are more common in elderly
Renal function	Decreased renal function may increase the risk for adverse effects
Genotype for CYP, UGT, transporters etc.	Some interactions may occur only in some patients
Dose	Some interactions do not occur with low doses.
Gender	QT-prolongation is more common in women
Plasma levels of drugs	Warnings could be diminished if it is known that the patients concentration is within the therapeutic interval
Other measurements such as serum potassium	Warnings should be given only when potassium is not measured or high.

Table 4. Examples of factors registered in the health care records that in the future could be used to decrease over-alerting.

6 FUTURE PERSPECTIVES

Drug-drug interactions will continue to be a problem for drug prescribers and dispensing pharmacists. The prevalence of drug-drug interactions will probably increase, due to increasing polypharmacy, and more sophisticated methods for identifying and handling drug-drug interactions will have to be developed. Today many physicians are not aware of what drugs a patient is using, making it almost impossible for them to know of potential drug-drug interactions. In an ongoing study we attempt to quantify this problem using data on prescriptions patients have received both from their primary health care centers and from other prescribers. In Sweden there is an ongoing project to develop a national database of medication orders. The aim of this database is to store all the patients' medication orders and make the list reachable from all electronic health care systems used in the country. It is advisable to link a clinical decision support systems (including SFINX) to this complete drug list to support the users [195].

In this thesis we have evaluated the impact of SFINX on prescribing and analyzed user perception. The findings are interesting but there is much more that could be done to gain additional knowledge. The study investigating the impact of SFINX on prescribing of potentially serious drug-drug interactions could be done in a different setting with larger study groups. SFINX should then ideally be implemented in another manner and all users should be taught how to use the system. Another, even more interesting study, would be to actually track what actions users have taken according to the information in SFINX. This could be done either automatically logging all searches in the database or also logging all drugs prescribed. Another way would be to invite physicians to participate in a study where they are asked to give information about how they have specifically handled the certain interaction warnings they have received.

Regarding how the users perceive SFINX one should ideally perform another questionnaire study for users of SFINX integrated into the electronic health records. The questionnaire should have a focus on alert fatigue and overriding since this is the major problem with drug-drug interaction warning system. Interviews with users could also give more information on how SFINX is perceived.

The SFINX database could probably be improved by addition of more herbal drugs. Another feature that could be added to improve usefulness would be to add drug combinations with evidence for lack of interaction. This should of course be an on-demand feature and not something that the prescriber is forced to see. To avoid over-alerting other algorithms such as drug dosage or further patient specific data (kidney and/or liver function, certain genotypes) could be integrated into the system.

The interaction between lamotrigine and quetiapine should ideally be investigated in a cross-over study either in patients or in volunteers. The dependence of CYP2C9*3 on the interaction between simvastatin and warfarin should, if possible, be confirmed (or discarded) in a larger patient material. It would also be possible to make a clinical trial comparing patients with CYP2C9*1/*1 genotype to patients with CYP2C9*1/*3 genotype. The results from an in vitro study investigating if simvastatin is a selective inhibitor of CYP2C9*3 would be informative.

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