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INTERAKCIJE MED ZDRAVILI PRI GERIATRIČNIH BOLNIKIH IN ANALIZA DELOVANJA AVTOMATSKEGA SISTEMA ZA SPREMLJANJE INTERAKCIJ MED ZDRAVILI

DRUG-DRUG INTERACTIONS IN GERIATRIC PATIENTS AND ANALYSIS OF THE AUTOMATED DRUG-DRUG INTERACTION SYSTEM

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CONTENTS

1 ABSTRACT V

2 RAZŠIRJEN POVZETEK VI

3 ABBREVIATIONS XI

4 INTRODUCTION 1

4.1 DRUG RELATED PROBLEMS 1

4.1.1 Terminology and relationship between terms 1

4.1.2 Additional costs due to ADEs, ADRs and AEs 4

4.1.3 Drug interactions 5

4.2 REDUCTION OF ADEs 12

4.2.1 Computerized Physician Order Entry 12

4.2.2 Clinical Decision Support Systems 13

4.2.3 Advantages and disadvantages of CDSS 16

4.2.4 Effects of CPOE and CDSSs on drug safety 17

4.2.5 Cost reduction 17

5 AIMS AND OBJECTIVES 18

5.1 STUDY AIM 18

5.2 STUDY OBJECTIVES 18

5.2.1 Prospective study 18

5.2.2 Retrospective study 19

6 MATERIALS AND METHODS 19

6.1 MATERIALS 19

6.1.1 The hospital 19

6.1.2 Computerized Physician Order Entry 20

6.1.3 The hospital pharmacy 21

6.2 STUDY DESIGN 22

6.2.1 Prospective study 22

6.2.2 Retrospective study 23
6.2.3 Patient exclusion criteria 23
6.3 DATA COLLECTION 24
6.3.1 Prospective study 24
6.3.2 Retrospective study 24
6.4 ADVERSE DRUG EVENT ASSESSMENT 24
6.4.1 Prospective study 24
6.4.2 Retrospective study 25
6.5 STATISTICAL ANALYSIS 25
7 RESULTS 26
7.1 PROSPECTIVE STUDY 26
7.1.1 Possible drug-drug interactions 27
7.1.2 Clinical pharmacists' interventions 31
7.1.3 Identified ADEs 31
7.2 RETROSPECTIVE STUDY 40
7.2.1 Risk of hyperkalemia 41
8 DISCUSSION 45
8.1 PROSPECTIVE STUDY 45
8.1.1 Identification of an ADE and causality assessment 45
8.1.2 Clinical pharmacists' interventions 46
8.1.3 Patient characteristics 46
8.1.4 Study limitations 47
8.2 RETROSPECTIVE STUDY 48
8.2.1 Risk of hyperkalemia 48
8.2.2 Study limitations 49
8.3 GENERAL DISCUSSION 50
8.4 RECOMMENDATIONS 51

9 CONCLUSIONS 52

10 BIBLIOGRAPHY 53

11 ATTACHMENTS 57

ATTACHMENT 1: ELECTRONIC PRESCRIPTION 57
ATTACHMENT 2: WEEKLY REPORT ABOUT DRUG-DRUG ALERTS 58
ATTACHMENT 3: CLINICAL PHARMACIST'S INTERVENTION AS ELECTRONIC MESSAGE VIA THE EMD 65
ATTACHMENT 4: CLINICAL PHARMACIST'S INTERVENTION AS PAPER DOCUMENT 66
ATTACHMENT 5: INTERACTIONS CHECK REPORT 67
ATTACHMENT 6: ATC CLASSIFICATION 69

FIGURES

Figure 1 Relationship between ADEs, ADRs and MEs 2

Figure 2 Relationship between ADEs, ADRs and MEs 3

Figure 3 Patient's hospitalization overview in the EMD 20

Figure 4 Drug-drug interaction alert in the CWS 21

Figure 5 Prescribed drugs according to the ATC classification 26

Figure 6 Amount of drug-drug interactions with respect to the number of drugs prescribed 27

Figure 7 Frequency of alerts according to potassium concentration 41

Figure 8 Frequency of overridden and accepted alerts according to potassium concentration 42

Figure 9 Chi-Square tests 43

Figure 10 Crosstabulation (acceptance of alert and potassium product) 43

Figure 11 Oral and i.v. potassium supplements according to potassium concentration 44

TABLES

Table I Age-related physiological changes in pharmacokinetics 6

Table II Classification of interactions according to the risk rating in Lexi-Comp Online™ 10

Table III Classification of actions (Stockley's) 11

Table IV Classification of interactions in Delphi Care 12

Table V Advantages and disadvantages of CDSS 16

Table VI Causality assessment of suspected adverse drug reactions 25

Table VII The most common interactions of type C identified when reviewing therapy .. 28

Table VIII The most common interactions of type D identified when reviewing therapy 29

Table IX Interaction of type X 30

Table X Number and type of clinical pharmacists' intervention 31

Table XI Causality assessment of suspected ADEs 32

Table XII Identified ADEs with causality assessment (certain, likely and possible) 33

Table XIII DDIs responsible for an ADE, divided per drug group 39

Table XIV Alerts generated by CDSS 40

1 ABSTRACT

Drug-drug interactions in elderly represent a major problem due to polypharmcy and physiological changes associated with aging that affect pharmacokinetics and pharmacodynamics. Therefore inadequate therapy often leads to adverse drug events (ADEs) which can be prevented by information technology support.

The aim of this study was to analyse the results and the performance of the automated interaction check system that is implemented in the computerized physician order entry system of the UZ Brussel in order to identify current problems and shortcomings. This was investigated in a prospective and retrospective manner.

In the prospective study, 50 patients from the geriatric ward were included. After the clinical pharmacists acquired the medication history, an interaction-check with Lexi-Interact Online™ was performed. If an interaction was judged clinically relevant, an intervention was conducted. The causality of suspected adverse drug events was assessed by an independent clinical pharmacologist. In the retrospective study, the drug-drug interaction alert reports for a period of 18 months were reviewed and the alerts were categorized according to the type of interaction risk. Where this was relevant, the laboratory results were checked.

In the prospective study, the median age of the included patients was 84.5 years (75 to 94) (68.0% female). We identified 257 drug-drug interactions (DDIs) of type C (Monitor therapy), 47 interactions of type D (Consider therapy modification) and 2 interactions of type X (Avoid combination). Clinical pharmacists conducted 14 interventions for potential ADEs due to interacting drug combinations. A total of 45 ADEs were identified in 31 patients (6.7% of ADEs certainly, 51.1% of ADEs likely, 22.2% of ADEs possibly, and 20.0% of ADEs unlikely attributable to DDIs). Symptoms that most often occurred were falls (20.4%) and hypotension (18.5%). In the retrospective study, 2890 alerts were generated by the DDI module and 82.1% of them were overridden. The most common alert (72.1%) was a warning for the risk of hyperkalemia. However, 62.7% of these alerts were generated when the patient's potassium level was too low.

The study showed that adverse drug events occur frequently in the elderly and can be reduced by clinical pharmacists' interventions. An automated alert system can improve

patient safety but can also cause alert fatigue if the rate of overridden alerts is too high. Therefore, it is important to fine-tune the alerts in such a way that they are only appearing when clinically relevant.

2 RAZŠIRJEN POVZETEK

Uvod: Naraščajoče število zdravil in njihovih uporabnikov, nepravilno jemanje in povečevanje števila bolnikov s kroničnimi boleznimi pogostokrat vodijo v težave povezane z zdravili. V objavljeni literaturi najdemo različne definicije teh težav. Neželeni dogodek zdravljenja je definiran kot vsak neugoden zdravstveni dogodek, ki se pojavi med zdravljenjem z zdravili, vendar ni nujno vzročno povezan z zdravilom (3). Znano je, da so neželeni dogodki vzrok za višje stroške zdravljenja in predstavljajo pomembno breme današnjega zdravstvenega sistema. Eden izmed pogostih vzrokov za neželeni dogodek zdravljenja so interakcije med zdravili, ki pa jih je mogoče napovedati na podlagi kliničnih študij, poročil o kliničnih primerih in ob upoštevanju farmakoloških principov. K pojavu neželenih dogodkov so še posebej nagnjeni starostniki zaradi polifarmakoterapije, več sočasnih bolezni ter fizioloških starostnih sprememb, ki vplivajo na farmakokinetiko in farmakodinamiko zdravil. Interakcije med zdravili so definirane kot farmakokinetični ali farmakodinamični vpliv ene učinkovine na drugo, kar lahko privede do zmanjšane učinkovitosti ali povečane toksičnosti (17). Interakcije razdelimo na farmakokinetične in farmakodinamične. Farmakokinetične interakcije se lahko pojavijo v kateremkoli izmed procesov ADME (absorpcija, distribucija, metabolizem in eliminacija). Farmakodinamične interakcije se pojavijo, kadar imata 2 učinkovini aditiven ali sinergističen farmakološki učinek ali pa delujeta antagonistično. Interakcije označujemo glede na klinično pomembnost. Poznamo več različnih klasifikacij, in sicer v Sloveniji uporabljamo naslednjo: A (ni znane interakcije), B (ni potrebno ukrepanje), C (potrebna je kontrola terapije), D (priporoča se zamenjava oz. sprememba terapije) in X (izogibanje kombinaciji, izjemno nevarna interakcija). Da bi preprečili napake pri zdravljenju in izboljšali stroškovno učinkovitost, je na voljo podpora informacijskih sistemov, s pomočjo katere lahko neželene dogodke v veliki meri preprečimo. Ena izmed takih informacijskih podpor so sistemi za podporo pri kliničnem odločanju, ki so vgrajeni v elektronsko predpisovanje. Zagotavljajo svetovanje o odmerkih zdravil, načinu aplikacije, pregled alergij na zdravila in podvajanja terapije in drugo. Vsebujejo tudi avtomatsko spremljanje interakcij med

zdravili. Ta sistem za podporo pri kliničnem odločanju lahko pripomore zdravnikom k zmanjšanemu predpisovanju kontraindiciranih zdravil ter pomaga k prepoznavanju interakcij med zdravili (28). Medtem ko so opozorila, ki jih generira sistem za spremljanje interakcij med zdravili, lahko zelo koristna, se lahko hkrati pojavijo tudi tista, ki so klinično nepomembna. To lahko privede do t. i. »alert fatigue«, ko zdravniki ob pojavu prevelikega števila opozoril začnejo razveljavljati tudi tista opozorila, ki se lahko nanašajo na življenjsko ogrožujoče situacije. Čeprav so opozorila učinkovito orodje za varnejše predpisovanje zdravil, je potrebna nadaljnja izboljšava, da bi dosegli čim večje zmanjšanje preprečljivih napak.

Namen: Analizirati rezultate in zmogljivost avtomatskega sistema za spremljanje interakcij med zdravili ter identificirati obstoječe težave in pomanjkljivosti. To smo raziskali s prospektivno in retrospektivno študijo.

Materiali in metodologija: Študijo smo izvedli v univerzitetni bolnišnici *Universitair Zikenhuis Brussel* v Belgiji, ki je terciarna bolnišnica s 729 posteljami. Bolnišnica je razvila svoj računalniški sistem, imenovan klinične delovne postaje, ki je integriran na vseh oddelkih. Ta sistem vsebuje različne komponente, med drugim tudi elektronske zdravstvene kartoteke, elektronsko predpisovanje in sisteme za podporo pri kliničnem odločanju. Zdravniki predpisujejo zdravila preko elektronskega predpisovanja, elektronski recept pa je avtomatsko natisnjen v lekarni. Zdravila se izdajajo na pacienta, in sicer to delo opravljajo farmacevtski tehniki pod nadzorom bolnišničnih farmacevtov. Poleg dela v bolnišnični lekarni 3 farmacevtke opravljajo tudi delo kliničnega farmacevta na geriatričnem oddelku, kjer pregledajo bolnikovo terapijo in sestavijo zgodovino zdravljenja z zdravili. Če opazijo neskladja ali druge težave povezane z zdravili, opravijo farmacevtsko intervencijo. Računalniški sistem poleg elektronskega predpisovanja vsebuje tudi enega izmed sistemov za podporo pri kliničnem odločanju, in sicer je to avtomatski sistem za spremljanje interakcij med zdravili. Ta sistem preverja interakcije, ko je predpisano novo zdravilo, in upošteva vsa predpisana zdravila v obdobju zadnjih 3 dni. Morebitno opozorilo, ki se pojavi na ekranu v trenutku predpisovanja, lahko zdravnik upošteva ali ne. Sistem se aktivira, če novo predpisano zdravilo vstopa v interakcijo, ki spada v eno izmed dveh najbolj klinično pomembnih skupin interakcij (kontraindicirana kombinacija ali zaradi previdnosti kontraindicirana kombinacija). Vsak ponedeljek bolnišnična služba za informacijsko tehnologijo pošlje poročilo o vseh generiranih

opozorilih preteklega tedna oddelku za klinično farmakologijo in farmakoterapijo. V prospektivno študijo so bili vključeni bolniki z geriatričnega oddelka. Klinična farmacevtka je opravila pregled terapije in sestavila zgodovino zdravljenja z zdravili ter predlagala odpravo morebitnih neskladnosti s farmacevtsko intervencijo. Po približno 24 urah smo opravili pregled terapije z zdravili glede na interakcije med njimi s pomočjo programa Lexi-Interact Online™. V poročilo smo vključili interakcije tipa C, D in X in na podlagi poročila so klinične farmacevtke izvedle farmacevtsko intervencijo, če so interakcije ocenile kot klinično pomembne. Poročale pa so tudi o interakcijah, ki so se morebiti klinično izrazile še preden je bila izvedena intervencija. Pri pregledu elektronske zdravstvene kartoteke smo identificirali neželene dogodke zdravljenja. Povezavo med neželenim dogodkom in interakcijami med zdravili je ocenil klinični farmakolog (neocenljiva, pogojna, malo verjetna, možna, verjetna, nedvomna). V retrospektivni študiji smo pregledali poročila o generiranih opozorilih od 1. 1. 2010 do 30. 6. 2011 ter opozorila kategorizirali glede na tip tveganja, ki ga predstavlja interakcija. Če je bilo to potrebno, smo pregledali tudi laboratorijske izvide bolnikov. Zbrane podatke smo statistično analizirali s pomočjo programa IBM SPSS Statistics 20.0 in Microsoft Excel 2007.

Rezultati: V prospektivno študijo je bilo vključenih 50 bolnikov. Mediana starosti obravnavanih bolnikov je bila 84,5 let, od tega je bilo 68,0 % bolnikov ženskega spola. V povprečju so bolniki prejemali 8 zdravil. Najbolj pogosto predpisana zdravila so bila iz skupine C (27,2 %) po ATC klasifikaciji, sledila so zdravila iz skupine N (22,0 %) in A (20,2 %). Pri pregledu terapij smo med zdravili ugotovili 257 interakcij tipa C, 47 interakcij tipa D in 2 interakciji tipa X. Klinične farmacevtke so izvedle 14 intervencij za preprečitev potencialnih neželenih dogodkov, povezanih z interakcijami na podlagi naših poročil (7 od 9 je bilo sprejetih; za 5 intervencij, ki so vsebovale nasvet o spremljanju bolnika, nismo mogli preveriti upoštevanja intervencije). Med študijo smo identificirali 45 neželenih dogodkov povezanih z interakcijami. 13 od teh se je zgodilo še preden je bil bolnik sprejet v bolnišnico. 3 neželeni dogodki so bili ocenjeni kot nedvomno, 23 kot verjetno, 10 kot možno in 9 kot malo verjetno povezani z interakcijami med zdravili. Pri 11 pacientih so bile težave povezane z zdravili tudi vzrok za hospitalizacijo. Zdravilne učinkovine, ki so najpogosteje vstopale v interakcije, so spadale v skupino ACE inhibitorjev, sledili so jim diuretiki, beta-blokatorji in benzodiazepini. Simptomi neželenih dogodkov, ki so se najpogosteje pojavljali, so bili padci in hipotenzija, pogosti pa so bili

tudi bradikardija, omotica, zmedenost, agresivnost, izguba zavesti in poslabšanje ledvične funkcije. Med retrospektivno študijo je bilo generiranih 2890 opozoril za interakcije med zdravili in 82,1 % jih ni bilo upoštevanih. Najbolj pogosto opozorilo (72,1 %) je bilo opozorilo za nevarnost hiperkaliemije, in sicer za kombinacijo kalijevih dodatkov in diuretikov, ki varčujejo s kalijem. To opozorilo je bilo generirano za 646 bolnikov. 62.7 % opozoril je bilo generiranih za bolnike, ko je bila njihova serumska koncentracija kalija pod spodnjo mejo 3,6 mEq/L, 36.1 %, ko je bila koncentracija znotraj predpisanih meja in 1.2 %, ko je bila koncentracija nad zgornjo mejo 5,0 mEq/L. V povprečju je bila serumska koncentracija 3,4 mEq/L, kar je pod predpisano spodnjo mejo. Če je bila serumska koncentracija kalija znotraj meja ali nad 5,0 mEq/L, smo pregledali izvide v dneh po opozorilu. V 540 od 811 primerih vrednost kalija ni presegla zgornje meje in le v 3,2 % se je vrednost v 2 dneh po opozorilu dvignila nad 5,0 mEq/L. S Chi-kvadrat testom smo ugotovili, da sta spremenljivki (vrsta aplikacije kalijevega dodatka in sprejetost opozorila) statistično značilno povezani ($p = 0,010$). V primerih, kjer je v interakcijo vstopal per os kalijev dodatek, ni bilo sprejetih 87.9 % opozoril, ko pa je bil povod za opozorilo intravenski pripravek, ni bilo sprejetih 84.0 % opozoril.

Diskusija: Med prospektivno študijo smo zaradi možnosti manjkajočih podatkov v bolnikovi elektronski zdravstveni kartoteki o konkretnih težavah povezanih z zdravili povprašali tako zdravnika kot tudi bolnika. Da bi povečali zanesljivost študije, smo vse primere neželenih dogodkov prediskutirali s kliničnimi farmacevtkami, ki so sodelovale v študiji in s še 2 farmacevtoma (profesor in doktorski študent) z oddelka za klinično farmakologijo in farmakoterapijo. Neželene dogodke je ocenil samo en neodvisni ocenjevalec. Če bi oceno opravila dva ali več ocenjevalcev, bi s tem povečali zanesljivost rezultatov. Stopnja sprejetosti farmacevtskih intervencij je bila 77,8-odstotna, kar kaže na dovzetnost zdravnikov za farmacevtove predloge. Možno pa je, da je med izvajanjem intervencij prišlo do pojava pristranskosti. Ko je farmacevt predlagal spremembe pri zdravljenju, se je potencialno število interakcij zmanjšalo in posledično se je znižala pojavnost neželenih dogodkov. Če bi bolnike na geriatričnem oddelku razdelili v kontrolno in intervencijsko skupino ter intervencije v zvezi z interakcijami med zdravili izvajali zgolj v drugi skupini, to ne bi bilo etično. Rezultati retrospektivne študije so pokazali visoko stopnjo neupoštevanih opozoril, kar je postavilo vprašanje, zakaj zdravniki opozoril ne upoštevajo in kako izboljšati obstoječi sistem za avtomatsko spremljanje interakcij med

zdravili. V 62,7 % opozoril je bila serumska koncentracija kalija pod spodnjo mejo referenčnega območja, kar kaže na to, da je bila kombinacija kalijevega dodatka in s kalijem varčujočega diuretika kljub opozorilu predpisana varno. Vendar pa je težko oceniti, ali je laboratorijski izvid bolnika vplival na zdravnikovo odločitev, saj ni znano, ali je zdravnik videl laboratorijski izvid, preden je sprejel odločitev in ali je bil izvid v trenutku opozorila na voljo. Glede na visoko stopnjo neupoštevanih opozoril in hkratne prenizke serumske koncentracije kalija lahko sklepamo, da je glavna pomanjkljivost v tridnevnem obdobju pred opozorilom, za katerega sistem preveri predpisana zdravila in v katerem bolnik lahko že preneha jemati eno izmed kontraindiciranih zdravil. Zato je potrebna prilagoditev avtomatskega sistema za spremljanje interakcij, saj se je tridnevno obdobje v primeru tveganja za hiperkaliemijo izkazalo kot predolgo. Prav tako bi bil sistem bolj zanesljiv, če bi preverjal dejansko aplikacijo zdravil in ne zgolj predpisovanja.

Zaključki: Geriatrični bolniki so izpostavljeni velikemu številu potencialnih interakcij med zdravili zaradi polifarmakoterapije ter fizioloških sprememb, povezanih s staranjem, ki vplivajo na farmakokinetiko in farmakodinamiko učinkovin, zato so pri njih neželeni dogodki pogosti. Avtomatski sistem za spremljanje interakcij med zdravili je lahko dobro orodje za izboljšanje bolnikove varnosti, vendar le, če je pravilno zasnovan ter posledično učinkovit.

3 ABBREVIATIONS

ACE – Angiotensin-Converting Enzyme

ADE – Adverse Drug Event

ADME – Absorption Distribution Metabolism Excretion

ADR – Adverse Drug Reaction

AE – Adverse Event

ATC – Anatomical Therapeutic Chemical

CDS – Clinical Decision Support

CDSS – Clinical Decision Support System

CNS – Central Nervous System

CPOE – Computerized Physician Order Entry

CWS – Clinical Workstation

DDI – Drug-Drug Interaction

ED – Emergency Department

EMD – Elektronisch Medisch Dossier (Electronic Medical File)

EMR – Electronic Medical Record

EPS – Extrapyramidal Symptoms

FTE – Full Time Equivalents

HMG-CoA reductase – 3-hydroxy-3-methyl-glutaryl-CoA reductase

INR – International Normalized Ratio

IT – Information Technology

I.V. – Intravenous

LMWH – Low Molecular Weight Heparin

ME – Medication Error

SE – Standard Error

SSRI – Selective Serotonin Reuptake Inhibitor

VUB – Vrije Universiteit Brussel

WHO – World Health Organization

4 INTRODUCTION

First, the terms medication error (ME), adverse drug event (ADE), adverse drug reaction (ADR), and their correlation are described. Secondly, we present possible prevention strategies for medication errors (and consequently adverse drug events caused by MEs) with special focus on computerized physician order entry systems (CPOEs) and clinical decision support systems (CDSSs).

4.1 DRUG RELATED PROBLEMS

4.1.1 TERMINOLOGY AND RELATIONSHIP BETWEEN TERMS

MEDICATION ERROR

A medication error (ME) is defined as "any error in the prescribing, dispensing or administration of a drug, irrespective of whether such errors lead to adverse consequences or not" (1). This definition classifies errors according to where they occur in the medication use process. The most common errors are a result of poor prescribing (2) and include incorrect drug selection (wrong indication or contraindicated drug), wrong dosage regime, illegible handwriting, inaccurate medication history taking, confusion with the drug name, inappropriate use of decimal points, and the use of ambiguous abbreviations and verbal orders (1).

ADVERSE DRUG EVENT

An adverse drug event (ADE) is "any untoward medical occurrence that may present during the treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" (3). ADEs are categorized as actual or potential, preventable or non-preventable, ameliorable or non-ameliorable and error or non-error (see Figure 1 & 2) (4). A preventable adverse drug event is "an injury that is the result of an error at any stage in the medication use" (4). In a study where preventable ADEs were analyzed, a medication error occurred in the ordering stage in 49% of cases, in the administration stage in 26% of cases, in the dispensing stage in 14% of cases, and in the transcription in 11% of cases (total number of preventable ADEs and potential ADEs was

264) (2). The most common types of prescribing errors were wrong dose, followed by wrong choice, known allergy, wrong frequency and drug-drug interaction.

A non-preventable ADE is also known as an adverse drug reaction which can occur due to a side effect or an allergic reaction and is not caused by a medication error in the medication use cycle (4). An ameliorable ADE is "an injury of which the severity or duration could have been substantially reduced if different actions had been taken" (4). A potential ADE is "a medication error with the potential to cause an injury but which does not actually cause any injury, either because of specific circumstances, chance, or because the error is intercepted and corrected" (4). A potential ADE is always caused by a medication error while only a minority of MEs causes actual adverse drug events.

Adverse drug events are a frequent cause of hospital admission. They are common during hospital stay and are an important cause of morbidity and mortality. One third to one half of ADEs are caused by medication errors (1). In one study the incidence of ADEs was 6.5% in adult hospital admissions and 28% of these were judged preventable (2). However, incidence rates vary widely due to different definitions used. Many studies use the term adverse drug reactions which excludes ADEs that are caused by medication errors or they use another definition for adverse drug reaction.

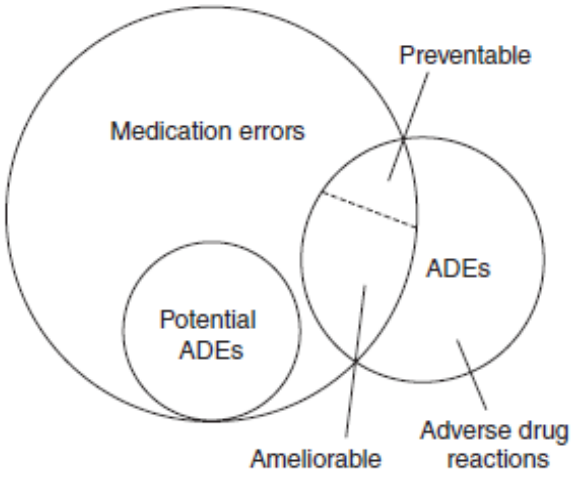

Figure 1 Relationship between ADEs, ADRs and MEs (4)

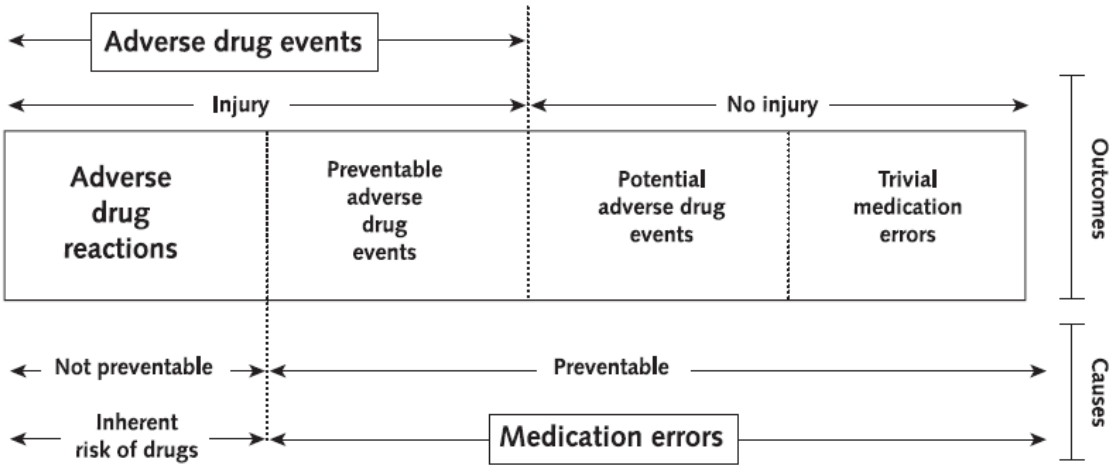

Figure 2 Relationship between ADEs, ADRs and MEs (6)

ADVERSE DRUG REACTION

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" (5). This includes only the appropriate use of drugs while most preventable drug-related injuries occur as a result of medication errors. A new classification of ADRs has been proposed recently although it has not yet been officially accepted because it is sometimes difficult or impossible to categorize an ADR as a type A or B (type A – dose dependent and predictable or type B – immunological or idiosyncratic reactions). Therefore, 4 categories (C to F) were added (5):

A. Dose-related (Augmented) – common, related to a pharmacological action of the drug, predictable, low mortality
B. Non-dose-related (Bizarre) – uncommon, not related to a pharmacological action of the drug, unpredictable, high mortality
C. Dose-related and time-related (Chronic) – uncommon, related to the cumulative dose
D. Time-related (Delayed) – uncommon, usually dose-related, occurs or becomes apparent some time after the use of the drug
E. Withdrawal (End of use) – uncommon, occurs soon after withdrawal of the drug
F. Unexpected failure of therapy (Failure) – common, dose related, often caused by drug interactions

4.1.2 ADDITIONAL COSTS DUE TO ADEs, ADRs AND AEs

It is well known that ADEs are directly associated with high medical costs and represent an important drug-related problem in health care systems of developed countries (2, 7, 8, 9, 10, 13). Adverse events can cause hospital admission, prolonged hospital stay, additional resource utilization, additional costs due to disability, lower patient satisfaction and patient harm.

Several studies in the USA and also in European countries have shown that the incidence of ADEs is relevantly high (7, 10). Different definitions and methods of detection have been used in various studies which explains the variation in incidence rates.

A meta-analysis performed in the United States (7) has shown that the overall incidence of serious ADRs is 6.7% and fatal ADRs appear to be between the fourth and sixth leading cause of death. In another study from the USA (8) it was established that 18 types of medical injuries were responsible for a total of 2.4 million extra days of hospitalization, $9.3 billion excess costs and 32591 deaths in the USA per year. For ADEs in particular, the extrapolated overall costs in the USA were estimated to be around $5.6 million for one hospital per year, and for preventable ADEs approximately $2.8 million per year (about half of the total, although they represent less than one third of all ADEs) (9). In one particular study (9), the length of hospital stay was on average 2.2 days longer for patients who experienced an ADE and on average 4.6 days longer for patients with a preventable ADE. Incidence rates of ADRs in Europe were even higher than in North America (10). Wiffen et al. (10) have done a systematic review of prospective and retrospective studies from 1966 to 1999 and established that the mean ADR rate was 4.6% in North American studies, 7.5% in British and Irish studies and 14.1% in European studies and the overall weighted ADR mean in all studies was 6.7%.

In Germany, the additional cost due to ADRs was estimated to be €400 million annually (11) and the projected annual cost of admissions related to ADRs in England was estimated at €706 million (12). In a recent study (13), which included 21 hospitals in the Netherlands, the mean excess length of stay due to adverse events (AEs) was estimated to be 10.1 days for university hospitals and 8.9 days in general hospitals. An adverse event is defined as an injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to

diagnose or treat, and the systems and equipment used to deliver care (14). Costs attributable to all AEs were estimated to be €355 million (2.4% of the national health care budget in 2004) and for preventable AEs €161 million (1.1% of the national health care budget in 2004). 2.3% of all hospital admissions were caused by preventable AEs and over 3% of all bed days were attributable to preventable AEs in 2004 (13).

No such study has been done in Slovenia, except for one (15), which evaluated the frequency of admissions to medical emergency departments (EDs) and hospitalizations due to ADRs detected by emergency physicians. 7% of the hospital admissions to the EDs of the University Medical Centre Ljubljana were caused by ADRs and extrapolated data suggest that 1200-1500 patients are hospitalized due to ADRs annually which represents an estimated €2.5–3 million of additional costs per year (16).

It seems clear that ADEs are associated with a significantly prolonged length of hospital stay, increased costs and increased mortality. Improvement of drug safety by preventing ADEs may be life-saving and cost effective.

4.1.3 DRUG INTERACTIONS

Drug interactions occur when the use of a drug results in a drug-drug, drug-food, drug-supplement or drug-disease interaction, which can lead to adverse events or decreased efficacy (17). They are often clinically unrecognized and responsible for important ADEs. Drug interactions can be predicted based on previous case reports, clinical studies and considerations of pharmacological principles. Fourteen studies assessed 62487 hospital admissions, 0.6% of which were caused by drug-drug interactions (DDIs). Within the subgroup of elderly patients it was estimated that DDIs were responsible for 4.8% of the admissions (18).

DRUG-DRUG INTERACTIONS IN THE ELDERLY

The elderly are particularly vulnerable for drug-drug interactions for several reasons. They often suffer from multiple morbidities and take several prescription and non-prescription drugs simultaneously. Polypharmacy significantly increases the risk of DDIs. A review indicated that patients older than 65 years use an average of 2 to 6 prescription medications and 1 to 3.4 non-prescription medications (18). It has been shown that clinically significant drug-drug interactions occur in 7% of patients taking 6 to 10 medications. If patients take

16 to 20 drugs, clinically significant interactions occur in 40% of patients (19). The toxicity of drug combinations is sometimes synergistic and is greater than the sum of the toxicity of each drug alone. DDIs are often not recognized in clinical practice which may trigger the prescribing of additional medication instead of adapting the dose of interacting drugs or discontinuing them.

Diseases and alteration in physiology place elderly patients at higher risk of adverse drug events due to DDIs. Renal elimination and liver metabolism are usually impaired (Table I) which influences the drug pharmacokinetics and consequently overdosing can occur when drug interactions increase the available amount of drug. This is especially dangerous for drugs with a narrow therapeutic index (e.g. lithium, digoxin, aminoglycosides). In such cases, careful dose titration and monitoring of the plasma drug concentrations is advisable.

Table I Age-related physiological changes in pharmacokinetics (20)

Parameter	Change	Effect
Absorption	Increased gastric pH Delayed gastric emptying Reduced splanchnic blood flow Decreased absorption surface Decreased gastrointestinal motility	Slightly decreased absorption (rarely clinically significant)
Distribution	Increased body fat (20–40%) Decreased lean body mass (10–15%) Decreased total body water (10–15%) Decreased serum albumin Increased α1-acid glycoprotein	Increased V_D and $t_{½}$ of lipophilic drugs Increased plasma concentration of hydrophilic drugs Increased free fraction in plasma of highly protein-bound acidic drugs Decreased free fraction of basic drugs
Metabolism	Decreased hepatic blood flow (20–50%) Decreased hepatic mass (20–30%)	First-pass metabolism can be less effective Phase I metabolism of some drugs might be slightly impaired
Excretion	Decreased renal blood flow Decreased glomerular filtration rate	Renal elimination of drugs can be impaired

A small change in the plasma drug concentration due to drug interactions can be significant because of age-related changes in pharmacodynamics. The change may occur at the receptor (e.g. change in the number and/or affinity of receptors), the signal transduction or the homeostatic mechanisms level. The central nervous system (CNS) and cardiovascular system are particularly vulnerable drug targets in the elderly. Between the age of 20 and 80 years, brain weight is reduced by 20% and neuronal loss has been reported for several brain regions (21). Elderly patients are also particularly sensitive to the effects of anticholinergic drugs, tricyclic antidepressants and anaesthetics (20). Also, a reduction in β-adrenoreceptors is typical for the elderly and consequently the sensitivity of the myocardium to catecholamines is lower and the effect of β-blockers is therefore diminished (21).

Other reasons for a higher risk of ADEs (resulting from DDIs) are the presence of multiple prescribers, poor compliance in the elderly which is associated with chronic disorders (that is when a patient forget or neglect to take the prescribed dosages at the recommended times or decide to discontinue the drug without consulting the physician), complex regimens, mistrust in drug effects, fear of ADRs, costs of medications, forgetfulness, cognitive disturbances and visual and/or hearing impairments (20).

MECHANISM OF DRUG-DRUG INTERACTIONS

A drug-drug interaction is defined as "a pharmacokinetic or pharmacodynamic influence of drugs on each other, which can result in reduced effectiveness or increased toxicity" (18).

PHARMACOKINETIC INTERACTIONS

Drug-drug interactions can occur in any stage of the ADME processes (22):

- Altered drug absorption can occur because of adsorption, chelation or other complexing mechanisms, changes in pH or changes in gastrointestinal motility. Usually these changes result in reduction of the absorption of orally administrated drugs. The binding of one drug to another is the most predictable interaction due to knowledge of their chemical characteristics. The classic example is the binding of tetracycline to calcium and magnesium containing antacids. The passage of drugs through mucous membranes of the gastrointestinal tract depends on the form (ionised or non-ionised) and medication that changes the gastric pH can significantly alter the rate of absorbed

drugs with acidic or basic characteristics or can cause dissolution of an enteric-coated product. Most drugs are absorbed in the upper part of the small intestine and agents that alter the transit time (e.g. anticholinergics) can influence the rate of drug absorption.

- Altered drug distribution usually occurs because of competitive inhibition for protein (particularly albumin) binding sites. The most important interactions include drugs, which are highly bound and have a narrow therapeutic index (e.g. warfarin). If a bounded molecule is displaced by a competitive drug, its plasma concentration may become toxic. Induction or inhibition of drug transporter proteins can be clinically significant for drugs that are actively transported by proteins such as P-glycoprotein and can result in decreased or increased uptake of substrates where P-glycoprotein is present in large amounts (e.g. distribution of drugs into the brain).

- The most important drug-drug interactions are those altering the metabolism. Drugs are metabolised in the serum, the kidneys, the skin and the intestine, but the major metabolism is performed in the liver. Phase I reactions (oxidation, reduction and hydrolysis) are carried out by cytochrome P (CYP)450 enzymes. More than 50% of drugs are metabolized by CYP3A4, which is one of the isoenzymes of the CYP450 system. Hepatic CYP3A4 declines with 8% per decade in older adults (23), and that is especially relevant in elderly patients. Medications that induce or inhibit CYP450 isoenzymes can cause decreased or increased effects of drugs metabolised by CYP450 and monitoring is advised when a CYP inhibitor is initiated or when the dose is increased.

- Most of the drugs are excreted in the urine through glomerular filtration and/or active tubular secretion. Altered drug elimination is associated with competition of two drugs for the same active secretion site of the tubule which may lead to decreased elimination of one of them and consequently a potential toxic serum concentration. Agents that inhibit the production of renal vasodilatory prostaglandins (e.g. NSAIDs) can cause changes in renal blood flow and therefore influence the excretion of drugs. In the elderly, drug-drug interactions that decline the renal function are also more significant due to age-related physiology changes. Alteration in urine pH can also affect drug elimination. Alkalinization of the urine increases the elimination of drugs that are weak

acids and decreases the elimination of weak bases. Acidification of the urine has the opposite effect.

PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic interactions occur when two or more drugs are used simultaneously that have additive or synergistic pharmacological effects or antagonistic pharmacological effects. Pharmacodynamic interactions are more common to cause ADEs than pharmacokinetic interactions. Pharmacodynamic interactions can be prevented more easily, if the pharmacologic principles are considered and the patient is monitored properly.

- Additive or synergistic interactions can sometimes be used intentionally. The concomitant use of two or more drugs is often clinically appropriate, but it is also important to recognize that the risk of adverse effects can increase (e.g. CNS depressants, sulfonylurea and metformin). In some cases, the use of a combination of interacting drugs is precautionary contraindicated because the result of the interaction can be life-threatening due to synergistic effects (e.g. neuromuscular blockers in combination with other drugs with neuromuscular blocking effects, concomitant use of drugs that prolong the QT interval).

- In contrast to additive interactions, there are some drug combinations with the opposite effect, i.e. antagonistic pharmacological effects. These combinations are sometimes contraindicated or adjustment of the dose or monitoring is necessary (e.g. ACE inhibitors and NSAIDs, anticoagulants and vitamin K, antidiabetics and glucocorticoids, antineoplastics and megestrol, levodopa and antipsychotics with dopamine antagonistic effects). (22)

CLASSIFICATION OF INTERACTIONS

Not all of the DDIs are clinically relevant and only a part of them has potential clinical consequences. Hence, a classification of interactions is required to support the practitioners' decision making in practice. Due to polypharmacy, it is very difficult for health care professionals to recognize all the potential interactions. Therefore, drug interaction software programs are available to help health care professionals.

LEXI-COMP ONLINE™

Lexi-Interact Online™ is a drug-drug, drug-herb and herb-herb interaction analysis program and combines the literature and scientific understanding of drug interactions from all around the world. A drug-drug interaction report includes the patient management information, the interacting members, the risk rating (Table II) and references.

Table II Classification of interactions according to the risk rating in Lexi-Comp Online™ (24)

Risk Rating	Action	Description
A	*No Known Interaction*	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents.
B	*No Action Needed*	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.
C	*Monitor Therapy*	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	*Consider Therapy Modification*	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents.
X	*Avoid Combination*	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

STOCKLEY'S DRUG INTERACTIONS

Stockley's Drug Interactions is a resource on drug interactions, covering therapeutic drugs, proprietary medicines, herbal medicines, foodstuffs, drinks, pesticides, and drugs of abuse. It is published in print and electronic versions. The digital version is available on the web

as a part of Medicines Complete. The interaction monographs are divided into different sections: Clinical evidence, Mechanism, Importance and management and References. Stockley's Interaction Alerts include the classification of actions described in Table III (22).

Table III Classification of actions (Stockley's) (22)

Action	Description
No action	For interactions where no action is needed, or for drug pairs where no interaction occurs.
Informative	For interactions where close follow up or monitoring are probably not automatically warranted due to the low probability of an interaction, but where more information is given in the event of a problem.
Monitor	For interactions where the drug pair is valuable and no compensatory action is possible, but the patient needs to be monitored to assess the outcome. For interactions where biochemical or therapeutic drug monitoring is recommended and further action may be needed based on the results.
Adjust	For interactions where the interaction can be accommodated, but where it is recommended that either one of the drug is changed, or the dose is altered on initiating the combination.
Avoid	For interactions where a drug combination is best avoided. This will mainly be used to highlight contraindicated drug pairs.

DELPHI CARE

Delphi Care is a Belgian online application which can identify drug-drug interactions. It is possible to search by active ingredient or by the brand/generic name of the medication. The interaction monograph is a text file that includes the interaction group, the intervention class, the pharmacological effect, the interaction mechanism, the actions required, commentary and literature references. Interactions are divided into 6 intervention classes (Table IV) (25).

Table IV Classification of interactions in Delphi Care (25)

Risk Rating	Short description	Long description
1	*Contraindicated*	The combination is contraindicated – serious impact is likely.
2	*Precautionary contraindicated*	Precautionary contraindicated.
3	*Monitoring / adjustment(s)*	Monitoring of the patient or therapy modification(s) is required.
4	*Monitoring / adjustment(s) sometimes required*	In some cases, follow-up or adjustment(s) is required.
5	*Follow-up as precaution*	Follow up the patient as a precaution.
6	*No action*	Actions are usually not required.

4.2 REDUCTION OF ADEs

In order to prevent medication errors and improve the cost effectiveness of drug therapies, technical solutions are available. Computerized physician order entry (CPOE) and clinical decision support systems (CDSSs) may reduce MEs, which can cause preventable injuries. CPOE associated with CDSSs has been shown to reduce medication errors up to 81% (4).

Since most ADEs in the elderly are predictable and therefore potentially avoidable, careful use of medications and vigilant drug monitoring are essential to avoid ADEs.

4.2.1 COMPUTERIZED PHYSICIAN ORDER ENTRY

Computerized physician order entry (CPOE) refers to any computer-based system in which medication orders or other physician instructions (tests and procedures) are entered electronically and the medication orders are directly transmitted to the pharmacy. The use of a CPOE system can help in reducing common medication errors related to poor handwriting prescribing and can save additional costs due to preventable ADEs caused by these medication errors. The implementation of CPOE can be a challenging process because of several factors such as the required start-up capital, careful planning and training of the end-users.

4.2.2 CLINICAL DECISION SUPPORT SYSTEMS

Clinical decision support systems (CDSSs) are computer systems designed to support clinician decision making on individual patients at the point in time when these decisions are made (26). CDSS are currently built into almost all CPOEs. There are many types of systems that can potentially support clinical decisions. They can provide computerized advice regarding drug doses, routes, frequencies, drug allergy checks, drug-laboratory value checks, drug-drug interaction checks and other drug related aspects.

Different goals of CDSSs are (27):

- Improving patient safety through the reduction of medication errors and adverse events, and improving medication and test ordering.
- Improving the quality of care by: increasing clinicians' available time for direct patient care, increasing application of clinical pathways and guidelines, facilitating the use of up-to-date clinical evidence and improving clinical documentation and patient satisfaction.
- Improving the efficiency of health care delivery by reducing costs through faster order processing, reductions in test duplication, decreased adverse events, and changed patterns of drug prescribing favoring cheaper but equally effective generic brands.

CATEGORIES OF BASIC MEDICATION-RELATED DECISION SUPPORT (28)

- Drug-allergy checking (e.g. generation of an alert when a provider orders a medication to which the patient has an electronically documented allergy).
- Basic dosing guidance for medications (e.g. a list of appropriate doses, frequency, route of administration is offered).
- Formulary decision support (e.g. display a pop-up alert when the clinician attempts to order a non-formulary drug and provide a list of alternative formulary medications).
- Duplicate therapy checking (e.g. a warning to inform the prescriber is generated when the patient is already receiving the same medication or a different drug in the same therapeutic category).

- Drug-drug interaction checking (e.g. a drug interaction alert appears when the physician wants to prescribe interacting drugs).

CATEGORIES OF ADVANCED MEDICATION-RELATED DECISION SUPPORT (28)

- Advanced dosing guidance (support tools which take into account patient variation: e.g. the indication for the drug; patient's characteristics such as age, weight, height, physiologic status and co-morbidities; other medications taken and the patient's previous response to the drug).

- Advanced guidance for medication-associated laboratory testing (e.g. reminders for pre- and post-drug administration tests to assist physicians with drug monitoring).

- Advanced checking of drug-disease interactions and contraindications (e.g. alerting the clinicians at the time of ordering about relevant underlying conditions).

- Advanced drug-pregnancy alerting (alerts are generated for high teratogenic or relatively contraindicated medications in pregnancy).

DRUG-DRUG INTERACTION ALERTS

CDS systems can help physicians to avoid prescribing contraindicated drug combinations by alerting them at the time of ordering. Glassman et al. (29) established that automated drug-drug interaction alerts have the potential to increase clinicians' recognition of drug-drug interactions. 55% of the clinicians felt that DDI alerts improved their ability to prescribe safely after Computerized Patient Record System implementation (29). In a survey, after evaluating each series of common drug interactions pairs, clinicians were asked how much more confident would they feel generally about their answers, if they had received evidence-based drug-drug alerts when appropriate. 88% of them would have felt at least moderately more confident in their answers (29).

Alerts should include the names of the interacting drugs, a brief description of the interaction, optional links to more detailed information and an advice for management of the patient. Furthermore, drug alerts should be sensitive (e.g. providing information about all potentially important interactions) and specific (e.g. assuring that each alert is clinically important).

ALERT FATIGUE

Drug interaction checking, while found to be beneficial in many cases, can also generate clinically insignificant alerts. This can result in a so called "alert fatigue" when the physicians, after receiving too many alerts, start to override the alerts, even those involving potential life-threatening situations. In a recent review, it was stated that safety alerts were overridden by clinicians in 49–96% of cases (30). Payne et al. (31) found that 11% of all medication orders generated drug-drug, drug-allergy or other interaction alerts and that "critical" drug-drug interaction alerts were overridden in 88% of cases. ADEs were observed in 2.3%, 2.5% and 6% of the overridden alerts in studies with override rates of respectively 57%, 90% and 80% (30). Alert overriding can often be justified. A part of the overridden alerts concerned alerts for interactions between systemic and topical medications and alerts generated during medication prescription renewals (31), which were not always clinically relevant. If the patient has already been taking the interacting combination of drugs, it is less likely that the interaction is clinically significant, because it was already overruled. Poor specificity and sensitivity of drug-drug interaction alerts may be an important obstacle for achieving the most efficient outcomes. Other reasons for overriding the alerts are inappropriate orders, disagreement with the guidelines, lack of time, lack of understanding the importance of the warning, technological problems and unnecessary workflow interruption (30).

Although warnings are a tool to prescribe more safely and reduce medication errors, further improvement is needed on the manner in which alerts are presented to the clinicians to maximize reduction of preventable errors.

4.2.3 ADVANTAGES AND DISADVANTAGES OF CDSS

Table V Advantages and disadvantages of CDSS (32)

Advantages	Disadvantages
Automatic provision of relevant, personalized expert advice, expertise and recommendations sourced from up-to-date, best practice knowledge.	Lack of robustness and flexibility (systems, when faced with a problem not contained in their knowledge bases, cannot solve the problem, recognize their inability to solve the problem, nor develop a strategy for doing so) (33).
Reduce variation in the quality of care.	Can be perceived as a threat to clinical judgment.
Can support medical education and training.	Potential 'deskilling' effect.
Can help overcome problems of inefficient coding of data.	Promote over-reliance on software; limit clinicians' freedom to think.
Can be cost-effective after initial capital costs and update and maintenance costs.	Difficult to evaluate – lack of accepted evaluation standards.
Can supply clinical information anytime, anywhere it is needed.	Uncertain and untested ethical and legal status.
If integrated with an electronic medical record (EMR), can help streamline workflow (history taking, diagnosis, treatment) and encourage more efficient data gathering.	Usage can be time-consuming, possibly lead to longer clinical encounters and create extra work.
Can provide an audit trail and support research.	Costs: maintenance, support and training required after initial outlay.
Can maintain and improve consistency of care.	The clinician's experience and imagination cannot be duplicated in a computer application.
Can provide immediate feedback to patients.	

4.2.4 EFFECTS OF CPOE AND CDSSs ON DRUG SAFETY

Clinical decision support systems have shown to improve patient safety and reduce the cost of care. The reminder and alerting programs can potentially reduce medication errors at the prescribing stage and consequently minimize the occurrence of adverse drug events caused by MEs.

The first study about the impact of CPOE with CDSS (only basic decision support) assessed a 55% decrease in non-intercepted serious medication errors ($p = 0.01$) and a 17% decrease in preventable ADEs (not statistically significant, $p = 0.37$) (34). Another study has shown an 81% decrease in MEs and a 86% decrease in non-intercepted serious MEs compared to the situation before implementation of CPOE (35). Computerized antibiotic drug advice decreased rates of toxic serum levels, rationalized the choice of antibiotics and lowered the antibiotic-associated ADE rate (32). Similarly, a warfarin dosing program demonstrated lower rates of bleeding complications, but the result was not statistically significant ($p = 0.11$).

A systematic review was performed about the effects of computerized CDSSs on practitioner performance and patient outcomes (36). There were 29 studies of systems for drug dosing and prescribing included. Single-drug dosing was improved in 15 of 24 studies and 2 of the 18 systems assessing patient outcomes reported an improvement. Another 5 systems used CPOE for multidrug prescribing and 4 of these systems improved practitioner performance, but none improved patient outcomes. Another review has shown that CPOE linked with CDS significantly decreased ADE rates in 5 of the 10 studies (37). Till 2011, only 4 studies about the effect of CPOE with CDS on ADEs were performed (37, 38). Two of these established a statistically significant decrease in ADE rates (37).

4.2.5 COST REDUCTION

Despite all the beneficial effects of CPOE systems, it requires a large capital investment to develop and implement such systems. CPOE start-up costs for a 500-bed hospital are estimated at approximately $8 million with annual maintenance costs of $1.35 million (39). These costs include hardware, software, implementation (physical installation of the components, process redesigns and process improvements) and support (trainings and support after implementation).

Nevertheless, the implementation of these systems is beneficial and cost-effective. The Brigham and Women's Hospital estimated savings of $5 to $10 million per year attributable to CPOE implementation and they estimated the costs associated with preventable ADEs before CPOE implementation at $2.8 million annually (35). Additionally, the use of CPOE linked to a comprehensive electronic medical record system lowered the charges with $887 per admission (35). A CDSS in conjunction with CPOE can also reduce the length of the hospital stay (39) and can therefore lower the associated costs.

Numerous challenges must be overcome to realize the medication-related benefits of CDSSs within CPOE, but when the system is once implemented it can improve patient-safety and lower medication-related costs.

5 AIMS AND OBJECTIVES

5.1 STUDY AIM

The aim of this study was to analyse the results and the performance of the automated interaction check system that is implemented in the CPOE system of the UZ Brussel in order to identify current problems and shortcomings. This was investigated in a prospective and retrospective manner.

5.2 STUDY OBJECTIVES

5.2.1 PROSPECTIVE STUDY

Primary outcomes:

- The analysis of possible drug-drug interactions of type C, D and X (according to Lexi-Comp Online™) in patients admitted to the geriatric ward.
- The identification of patients with a suspected ADE possibly due to DDIs.

Secondary outcomes:

- The causality assessment of suspected adverse drug events.
- The number of hospital admissions due to an adverse drug event and the number of patients admitted with specific drug toxicity.

- The identification of possible relevant interactions that are not yet identified by the automated CDS system.

5.2.2 RETROSPECTIVE STUDY

- Number of overridden interaction alerts generated by the CDS system.
- The identification of possible non-relevant interaction alerts generated by the CDS system.
- Determine whether a link of the interaction check with the laboratory results' database is warranted.

6 MATERIALS AND METHODS

6.1 MATERIALS

6.1.1 THE HOSPITAL

The UZ Brussel is a tertiary university hospital with 729 beds situated in Jette (Brussels). It has a fully integrated computer system on all departments called the clinical workstation (CWS). This system is developed within the hospital. The CWS consists of several components such as a Computerized Physician Order Entry system, the patients' electronic medical file called Elektronisch Medisch Dossier or EMD (see Figure 3), a limited number of CDSS, etc. The EMD includes all possible information such as the patient's medical record, physician notes (see Figure 3), nurse notes, pharmacist intervention notes, laboratory results and medication information (both preadmission medications and medications prescribed at the hospital).

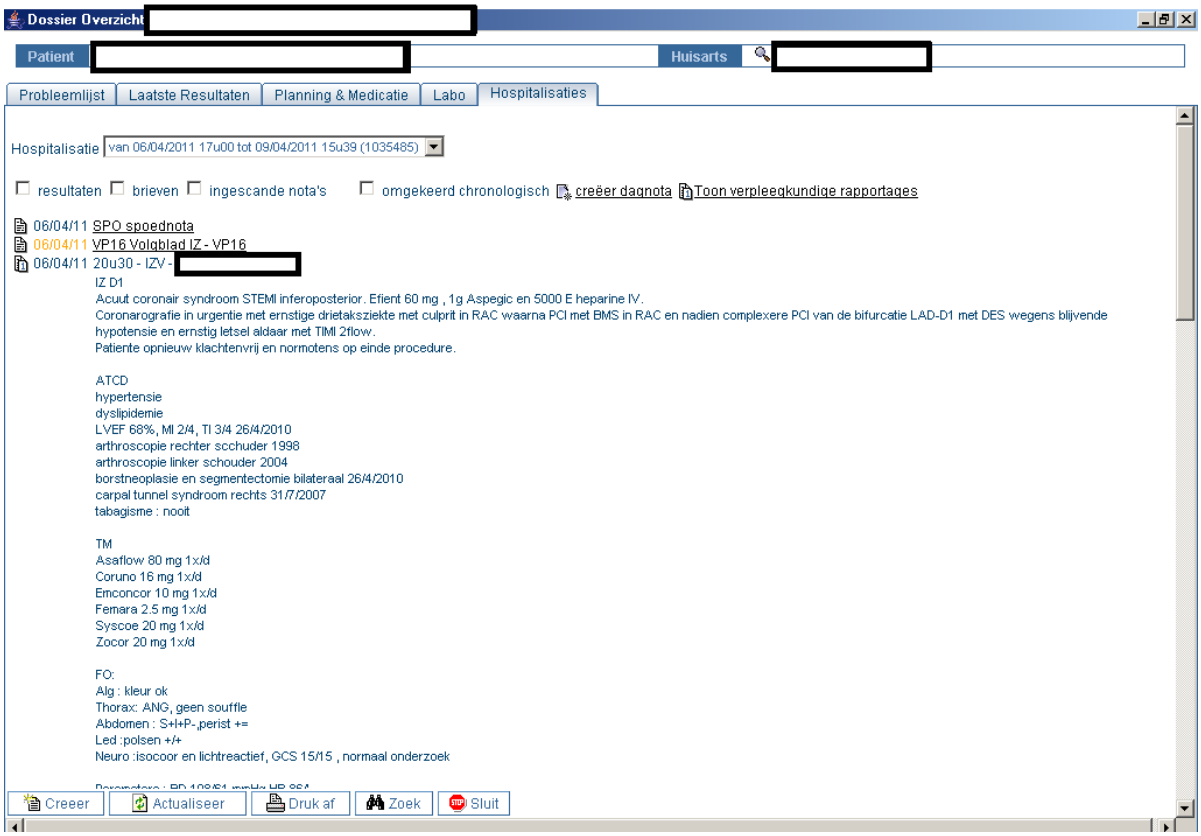

Figure 3 Patient's hospitalization overview in the EMD

6.1.2 COMPUTERIZED PHYSICIAN ORDER ENTRY

Drug orders are entered directly by the physician via the CPOE module. The electronic prescription (see Attachment 1) is automatically printed in the pharmacy. The regular prescriptions are handled by pharmacy technicians under supervision of a hospital pharmacist. Special non-formulary prescriptions or prescriptions for restricted medications are handled by hospital pharmacists. Medications are provided as unit doses which means that medications are dispensed as a single unit per patient. Usually unit doses for 3 days are provided. After 3 days, the prescription has to be renewed in order to continue the therapy.

A limited number of clinical decision support systems are built into the CWS and one of them is a drug-drug interaction check system. This system checks for interactions when a new drug is prescribed and takes already concomitantly given drugs and drugs given up to 3 days earlier into account. When the physician wants to prescribe an interacting drug, an interaction alert appears in real-time (see Figure 4). The system is activated for the 2 highest severity levels of interactions only in order to lower the number of alerts and to

reduce the chance for alert fatigue (type 1 = contraindicated combinations and type 2 = precautionary contraindicated combinations – according to Delphi Care) (25). Interaction alerts are non-interruptive and physicians can accept or override the alert.

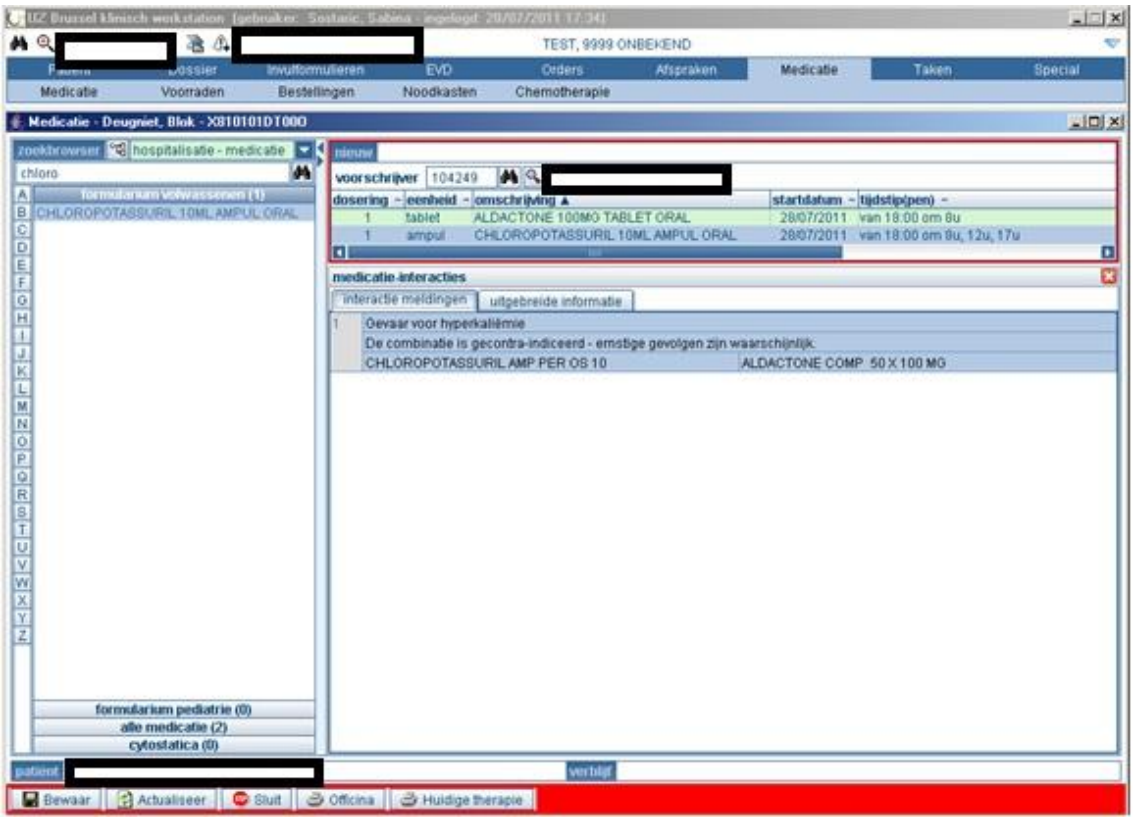

Figure 4 Drug-drug interaction alert in the CWS

Each Monday the Information Technology (IT) department of the hospital sends a report (see Attachment 2) of all the generated drug-drug interaction alerts for the past week. These reports include the interaction alerts generated for electronic prescriptions made on all departments. The reports are sent to all interested parties such as the Department of Clinical Pharmacology and Pharmacotherapy that coordinates drug policy and drug safety at the hospital.

6.1.3 THE HOSPITAL PHARMACY

The hospital pharmacy employs 10.8 full-time equivalent (FTE) hospital pharmacists, 1.8 FTE clinical pharmacists, 19.2 FTE technicians, 2.8 FTE for technical and production support, 5.8 FTE for administrative support, 1 FTE nurse as the head of the central sterilisation unit, which is part of the pharmacy, 2 FTE zone responsible persons in the

central sterilisation unit, 18.9 FTE sterilisation assistants and 4.6 FTE storage room personnel.

Besides working in the hospital pharmacy, 3 hospital pharmacists (together 1 FTE) work as clinical pharmacists at the geriatric ward. Each day of the week one of them participates in the morning meeting with the health care team. During these meetings, the head nurse informs other staff members about the patients' condition. After the meeting, the clinical pharmacists acquire and review the medication history of the patients admitted to the geriatric ward in the last 48 hours. If drug related problems (e.g. drug-drug interactions, oral dosage forms that should not be crushed, incorrect dosage etc.) are identified, an intervention is performed by the clinical pharmacists. These interventions are communicated by means of a phone call to the physician, an electronic message via the EMD in the patient's file overview (see Attachment 3), and with a yellow paper document inserted in the patient's non-electronic folder (see Attachment 4).

The 4th clinical pharmacist (0.8 FTE) is in charge of the follow-up of the antibiotic policy for all hospital wards. They work together with the microbiologists and infectiologists for the surveillance of patients under antibiotic therapy or prophylaxis.

6.2 STUDY DESIGN

6.2.1 PROSPECTIVE STUDY

A prospective study was conducted of patients admitted to the geriatric ward who were consecutively followed by the clinical pharmacists. After admission to the geriatric ward, the clinical pharmacists acquired the medication history by means of a structured interview and compared their acquired medication history with the physician-acquired medication history. Upon identification of a drug discrepancy, clinical pharmacists performed interventions to solve the discrepancies. After approximately 24 hours we performed a drug-drug interaction check (home medications + newly started therapy at the hospital) and sent a report (see Attachment 5) to the clinical pharmacists. This time interval was needed for allowing the physicians to apply the corrections made by the clinical pharmacists for possible discrepancies in the patient's medication history. The clinical pharmacists could then conduct an intervention for reported interactions that they judged clinically relevant. We checked the therapy for drug-drug interactions with the Lexi-Comp Online™

interaction database (24). Only interactions of type C (Monitor therapy), D (Consider therapy modification) and X (Avoid combination) were included in the report. If we could not find a medication in the Lexi-Comp Online™, we used the Stockley's online database (22). The classification of actions used in Stockley's Interaction Alerts is not exactly the same as in Lexi-Comp Online™, but the content is comparable. Therefore, we decided to count type C as "Monitor", type D as "Adjust" and type X as "Avoid" in Stockley's (22). We reviewed electronic nurses' and physicians' notes, the reason of admission, laboratory results and the medication charts during the hospital stay in order to detect ADEs or identify ADEs related to hospital admission. The clinical pharmacists also reported if any of the interactions occurred in practice before the intervention was made.

6.2.2 RETROSPECTIVE STUDY

We reviewed all the drug-drug interaction alert reports (see Attachment 2) generated by the system from 1st January 2010 till 30th June 2011. The alerts were categorized according to the type of interaction risk. We also checked the laboratory results in case this was relevant (e.g. the potassium level in case of an alert for the risk of hyperkalemia).

6.2.3 PATIENT EXCLUSION CRITERIA

PROSPECTIVE STUDY

Patients were excluded from the study

- whenever they died at the hospital,
- if the patient was given only 1 medication (DDI not possible),
- if there was no medication history available,
- if the patient was discharged the same day or the day after the interaction check report was made, because in this case we could not assure that the patient was followed long enough to make the assessment of an ADE.

RETROSPECTIVE STUDY

All the alerts form the weekly reports were included in the study, except for the alerts that refer to the test patients. Test patients are imaginary patients created in the CWS to test and improve the system.

6.3 DATA COLLECTION

6.3.1 PROSPECTIVE STUDY

Patients admitted to the geriatric ward from 2nd March till 9th June 2011 were included. The geriatric ward, consisting of 30 beds, was selected because of the high number of medications taken per patient and high susceptibility of geriatric patients for ADEs. The following information was recorded for all patients: the patient's identification number, gender, age, date of admission to the geriatric ward and the list of all the medications administrated at the hospital at the moment of performing the interaction check. The observation time was the time since the medication history was made till the end of the hospitalization.

6.3.2 RETROSPECTIVE STUDY

Data were obtained from the drug-drug interaction reports (see Attachment 2). The EMD was used to collect laboratory values.

6.4 ADVERSE DRUG EVENT ASSESSMENT

6.4.1 PROSPECTIVE STUDY

Patients with suspected adverse drug events were selected for further assessment after consultation with the clinical pharmacists. The causality assessment evaluator was a clinical pharmacologist who was previously not involved in the study. He was given a short overview of the clinical cases. He could also look up information in the patient's electronic files, nurses' notes and laboratory results. We were available for possible questions throughout the assessment period. The evaluator was referred to the article "Adverse drug reactions: definitions, diagnosis, and management" (40) for the causality assessment of suspected adverse drug events (see Table VI).

Table VI Causality assessment of suspected adverse drug reactions (40)

Certain	• A clinical event, including a laboratory test abnormality that occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. • The response to withdrawal of the drug (dechallenge) should be clinically plausible. • The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
Probable/likely	• A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). • Rechallenge information is not required to fulfil this definition.
Possible	• A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. • Information on drug withdrawal may be lacking or unclear.
Unlikely	• A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.
Conditional/ unclassified	• A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are being examined.
Unassessable/ unclassifiable	• A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified.

6.4.2 RETROSPECTIVE STUDY

An assessment of ADEs was not performed for the patients included in the retrospective study due to time limitations and the absence of clinical pharmacists' reviewed medication histories for most cases.

6.5 STATISTICAL ANALYSIS

Data gathered were analyzed with IBM SPSS Statistics 20.0 and Microsoft Excel 2007. The Chi-Square test was used for testing whether there's a relationship between two categorical variables. The statistical analysis was performed with a 0.05 significance level.

The frequency distributions of potassium levels were presented with histograms. Due to discrepancies in the collected data, we decided to choose 1 potassium level per day per alert. If there was more than one representative laboratory value per day, the first value was considered. If there were two values and one of the results was not reliable (due to hemolyzation), the reliable one was considered. In cases where there was only an unreliable result, this result was used. In one alert, no laboratory result was available. In cases where there were no recent laboratory values, alerts were excluded from the analysis.

7 RESULTS

7.1 PROSPECTIVE STUDY

During the study period 50 patients were included. The median age was 84.5 years (range 75 to 94 years). 34 (68%) patients were female and 16 (32%) male. The average number of drugs given to a patient was 8 (SE = 2.75). 10 patients were given 2 to 5 medications, 29 patients were given 6 to 9 medications, 9 patients were given 10 to 13 medications and 2 patients were given more than 13 medications. The most frequently prescribed medications among elderly were medications to treat cardiovascular diseases – anatomical therapeutic chemical (ATC) group C (27.2%). The second most commonly prescribed drugs were those to treat nervous system diseases – ATC group N (22.0%) and the third group consisted of medications to treat alimentary tract and metabolism disease – ATC group A (20.2%). Group A was followed by medications to treat blood diseases and blood forming organs – ATC group B (13.6%) (see Figure 5).

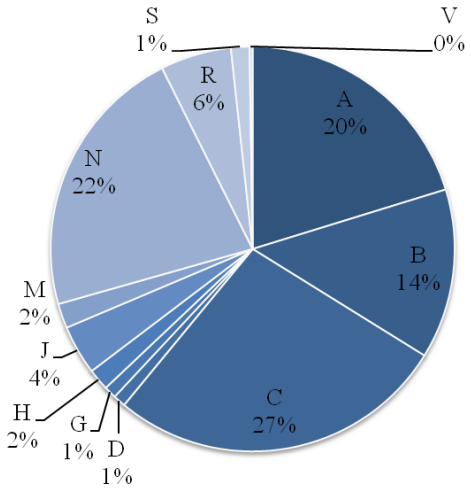

Figure 5 Prescribed drugs according to the ATC classification (see Attachment 6)

7.1.1 POSSIBLE DRUG-DRUG INTERACTIONS

During the data collection period 257 drug-drug interactions of type C, 47 interactions of type D and 2 interactions of type X were identified (24). In only one patient the prescribed medications did not trigger potential interactions. The incidence of potential drug-drug interactions increased as the number of total medications increased, ranging from 2.4 potential interactions for 2–5 drugs to 18 potential interactions for 13 or more medications (see Figure 6).

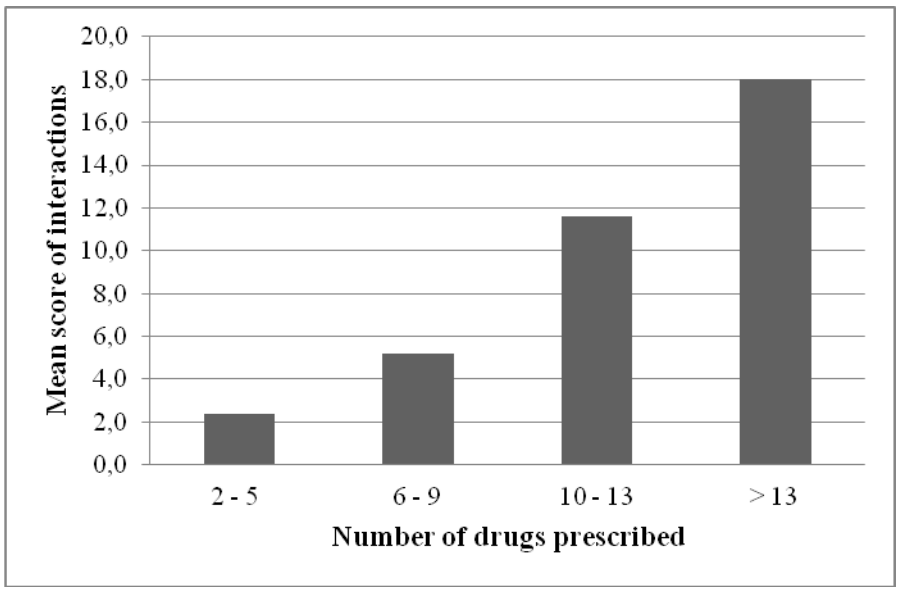

Figure 6 Amount of drug-drug interactions with respect to the number of drugs prescribed

DRUG-DRUG INTERACTIONS OF TYPE C

Drug combinations triggering drug-drug interactions of type C 4 or more times in all 50 patients, are summarized in Table VII.

Table VII The most common interactions of type C identified when reviewing therapy

DRUG COMBINATION	RECOMMENDATION IN Lexi-Comp Online™ (24)
ACETYLSALYCILIC ACID – NADROPARIN (N = 4) Salicylates may enhance the anticoagulant effect of anticoagulants.	To increase monitoring diligence for signs and symptoms of bleeding, if these agents are used concomitantly.
ACETYLSALICYLIC ACID – LISINOPRIL/RAMIPRIL (N = 5) Salicylates may diminish the antihypertensive effect of ACE inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of congestive heart failure. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE inhibitor efficacy.	To monitor for decreased therapeutic effects of ACE inhibitor if a salicylate is initiated or dose increased, or increased effects if a salicylate is discontinued or dose decreased. *All patients except 2 were given doses smaller than 100 mg/day.*
CALCIUM CARBONATE – SIMVASTATIN/PRAVASTATIN/ ATORVASTATIN/ROSUVASTATIN (N = 6) Calcium carbonate may decrease the serum concentration of HMG-CoA reductase inhibitors. This interaction is likely to be of greatest potential significance with regular use of $CaCO_3$.	To monitor for decreased effects of statins (e.g. cholesterol changes) in patients who consistently take $CaCO_3$ concomitantly. To space $CaCO_3$ use 2 hours or more after statin dosing.
CALCIUM CARBONATE – AMLODIPINE/LERCANIDIPINE (N = 7) Calcium salts may diminish the therapeutic effect of calcium channel blockers.	To monitor for decreased therapeutic effects of calcium channel blockers if a calcium supplement is initiated or dose increased, or increased effects if a calcium supplement is discontinued or dose decreased.
BUMETANIDE – LISINOPRIL/RAMIPRIL (N = 5) Loop diuretics may enhance the hypotensive effect of ACE inhibitors (specifically, postural hypotension which can accompany ACE inhibitor initiation). Loop diuretics may also enhance the nephrotoxic effect of ACE inhibitors.	To monitor for evidence of significant postural hypotension if an ACE inhibitor is initiated in patient already receiving a loop diuretic, especially if the patient has signs or symptoms of hypovolemia or hyponatremia. To ensure the patient remains supine for 3 or more hours following the administration of the first dose of the ACE inhibitor. To monitor for signs or symptoms of renal dysfunction if

	these two agents are used concomitantly long-term. To consider a reduced dosage of either the loop diuretic or ACE inhibitor if serum creatinine increases during concomitant therapy.
BUMETANIDE – BISOPROLOL/NEBIVOLOL (N = 4) Hypotensive agents may enhance the adverse effect of other hypotensive agents.	To monitor blood pressure, hemodynamic status and heart rate closely and advise patients regarding signs or symptoms of hypotension when two or more of these agents are used in combination.
BISOPROLOL – HUMAN INSULIN/ INSULIN GLARGINE (N = 5) Beta-blockers may enhance the hypoglycemic effect of insulin. Cardioselective beta-blockers (bisoprolol) may be safer than nonselective beta-blockers.	To monitor for increased therapeutic effects of insulin if a beta-blocker is initiated or dose increased or decreased effects if a beta-blocker is discontinued or dose decreased. To instruct patients that tachycardia, as a sign of hypoglycemia, may not be present.
OLANZAPINE – TRAZODONE (N = 4) Antipsychotics may enhance the serotonergic effect of serotonin modulators, which could result in serotonin syndrome.	To use caution with concurrent use of any serotonin modulator with an antipsychotic. To monitor patients extra closely for evidence of serotonin toxicity (e.g. mental status changes, autonomic instability, and neuromuscular hyperactivity) or neuroleptic malignant syndrome (e.g. hyperthermia, muscle rigidity, autonomic dysfunction).

DRUG-DRUG INTERACTIONS OF TYPE D

Interactions of type D that were identified 3 or more times are summarized in the following table. Drugs that often triggered interactions were acenocoumarol, allopurinol, calcium carbonate, escitalopram, lisinopril and trazodone.

Table VIII The most common interactions of type D identified when reviewing therapy

DRUG COMBINATION	RECOMMENDATION IN Lexi-Comp Online™ (24)
CALCIUM CARBONATE – LISINOPRIL/PERINDOPRIL (N = 5) Calcium salts may decrease the serum concentration of ACE inhibitors.	To monitor for decreased therapeutic effects of ACE inhibitors if a calcium salt is initiated or dose increased, or increased effects if a calcium salt is discontinued or dose decreased. *The United States and Canadian fosinopril manufacturer labelings both recommend separating the doses of antacids and fosinopril by at least 2 hours. Captopril bioavailability has been reported to be decreased by approximately one-*

	third when coadministered with an antacid containing aluminum hydroxide, magnesium carbonate, and magnesium hydroxide. The potential for other ACE inhibitors to be similarly affected is unknown.
CALCIUM CARBONATE – FERROUS GLUCONATE (N = 3) Calcium salts may decrease the absorption of iron salts.	To separate dosing of oral iron preparations and calcium salts by as much time as possible. To monitor for decreased therapeutic effects of oral iron preparations if a calcium salt is coadministered.
CALCIUM CARBONATE – LEVOTHYROXINE (N = 3) Calcium salts may diminish the therapeutic effect of thyroid products.	To separate the doses of the thyroid product and the oral calcium supplement by at least 4 hours. To monitor for decreased therapeutic effects of thyroid products if an oral calcium supplement is initiated or dose increased, or increased effects if an oral calcium supplement is discontinued or dose decreased.
ALLOPURINOL – LISINOPRIL/RAMIPRIL (N = 3) ACE inhibitors may enhance the potential for allergic or hypersensitivity reactions to allopurinol. The mechanism of this potential interaction is unknown.	To monitor for evidence of hypersensitivity reactions following the initiation of allopurinol therapy for at least 5 weeks if allopurinol must be used in an ACE inhibitor patient.

DRUG-DRUG INTERACTIONS OF TYPE X

Interactions of type X were found in 2 patients (see Table IX).

Table IX Interaction of type X

DRUG COMBINATION	RECOMMENDATION IN Lexi-Comp Online™ (24)
CLOPIDOGREL – OMEPRAZOLE (N = 2) Omeprazole may decrease serum concentrations of the active metabolite(s) of clopidogrel that undergoes CYP2C19-dependent activation.	To avoid concurrent use due to the possibility that combined use may result in decreased clopidogrel effectiveness and the availability of suitable alternatives for proton pump inhibitor therapy. *In one case omeprazole was substituted with pantoprazole which triggers an interaction of type D. Some small, prospective, non-randomized trials examining the effects of concurrent therapy of pantoprazole and clopidogrel in healthy subjects show that pantoprazole did not apperar to alter clopidogrel antiplatelet effects or only a small (but statistically significant) decrease in inhibition of platelet aggregation activity was found (23).*

7.1.2 CLINICAL PHARMACISTS' INTERVENTIONS

Clinical pharmacists conducted 14 interventions (26.0% of all patients) for 14 reported potential ADEs due to interacting drug combinations that they judged clinically relevant (see Table X). For one patient an intervention was performed based on an interaction that was found additionally with Stockley's online database that was not included in Lexi-Comp Online™ (interaction between amlodipine and lithium). Because possible drug related tremor was noted in the patient's file, the drug therapy was rechecked for possible interactions with Stockley's online database.

Table X Number and type of clinical pharmacists' intervention

Type of intervention	Number of interventions	Number of interventions accepted by the physicians
Monitor a patient's condition	5 (3 of them were related to higher risk of bleeding)	*We were not able to verify if the advice to monitor was accepted.*
Separate the doses of the interacting drugs in order to minimize an interaction	4	3
Stop one of the interacting drugs	2	2
Change an interacting drug to another one	2	1
Change the dose of one of the interacting drugs	1	1

7.1.3 IDENTIFIED ADEs

A total of 45 adverse drug events were identified in 31 patients (62.0%). 13 ADEs (28.9%) occured at home (1 assessed as certainly, 8 as likely, 3 as possibly and 1 as unlikely attributable to DDIs). It was judged that 6.7% of all 45 ADEs were certainly attributable to DDIs, 51.1% of them were likely attributable to DDIs and 22.2% of them were possibly attributable to DDIs. In 9 cases (20.0%) the ADE was unlikely to be caused by DDIs. Table XI summerises the causality assesment of all suspected ADEs.

Table XI Causality assessment of suspected ADEs (40)

Causality assessment	Number of ADEs
Certain	3
Likely	23
Possible	10
Unlikely	9
Conditional	0
Unassessable	0

In 11 of 50 patients (22.0%), medications were involved in the reason for hospital admission. 2 patients were admitted with specific drug toxicity (increased lithium and digoxin serum level). 9 other hospital admissions were related to ADEs attributable to DDIs (1 patient was admitted also due to a medication error that occurred in the nursing home). 7 of them were assessed as likely, 1 as certainly and 1 as possibly attributable to DDIs.

In 20 ADEs the DDI could be assigned to two drugs. Three or more drugs were involved in the remaining 16 ADEs assessed as possible, likely or certain (Table XII). ACE inhibitors were involved in 28 (19.7%) of the 142 DDIs (in 14 (9.9%) DDIs interacting with diuretics), followed by diuretics (19.0%, N = 27), beta-blockers (10.6%, N = 15) and benzodiazepines (7.7%, N = 11) (Table XIII). The total number of 142 DDIs includes DDIs involved in ADEs assessed as possible, likely or certain. 1 DDI presents a DDI between 2 drugs and if an ADE was related to a combination of 3 drugs, that means 3 DDIs in total.

Symptoms that most often occurred were falls (20.4%) and hypotension (18.5%) usually caused by the combination of several antihypertensive drugs or additive effects of different CNS depressants. Other common symptoms were bradycardia, dizziness, confusion, aggressiveness, loss of consciousness and renal failure.

Table XII Identified ADEs with causality assessment (certain, likely and possible)

PATIENT NUMBER	DRUG COMBINATION	POTENTIAL ADEs (according to Lexi-Comp Online™)	OBSERVED ADEs	ACTION AFTER AN ADE	CAUSALITY ASSESMENT
1	ALLOPURINOL – ACENOCOUMAROL (type D)	▪ increased prothrombin times if allopurinol is initiated or dose increased (increased risk of bleeding)	INR increased from 1.4 to 3.5 (allopurinol was home medication, acenocoumarol regimen was changed at the hospital)	Patient's INR was monitored. Daily dose of acenocoumarol was temporally stopped with INR normalization in the next days.	possible
	ACENOCOUMAROL – AMLODIPINE (type C)	▪ increased effects of acenocoumarol if amlodipine is initiated or dose increased (increased risk of bleeding)	INR increased to 3.9	Daily dose of acenocoumarol was temporally stopped. A day after the same regimen was continued, the INR normalized. Intervention for enhanced monitoring was made due to initiation of low cardioprotective aspirin doses and paracetamol prescribed if needed.	possible
2	BISOPROLOL – DONEPEZIL (type C)	▪ bradycardia ▪ hypotension	bradycardia	Bisoprolol was withdrawn.	possible
3	QUETIAPINE – RIVASTIGMINE (type C)	▪ neurotoxic effect of antipsychotics ▪ extrapyramidal symptoms (EPS)	rigidity, cogwheel rigidity	The physician did not change the therapy because both drugs were necessary for the patient's condition.	likely
	CALCIUM CARBONATE – HYDROCHLOROTHIAZIDE (type C)	▪ hypercalcemia ▪ metabolic alkalosis	hypercalcemia	After the pharmacist's intervention hydrochlorothiazide was stopped.	possible
4	PERINDOPRIL – CARVEDILOL/BISOPROLOL/ NEBIVOLOL – DONEPEZIL (type C)	▪ enhanced hypotensive effect ▪ altered hemodynamic status	hypotension	Physicians were trying to optimize the treatment of hypertension. Eventually they stopped all antihypertensive medication till hospital dismissal.	likely
5	PERINDOPRIL – ACEBUTOLOL (type C)		hypotension, 2 falls at home, complaints about	Both drugs were stopped in the hospital. The next day after admission an	likely

			dizziness and feeling that patient's blood pressure dropped (dizziness has begun since perindopril initiation).	orthostatic test was performed which was positive. In the following days blood pressure raised, therefore perindopril and a day later acebutolol were started again. Due to low blood pressure and dizziness, which occurred after re-initating the antihypertensive therapy, the doses of both medications were decreased. During hospitalization perindopril was stopped a second time because of declining kidney function and initiated again after an improvement. A week before hospital dismissal the patient was asymptomatically hypotensive.	
6	DIPYRIDAMOLE – FUROSEMIDE – SPIRONOLACTONE (type C)		hypotension (furosemide initiated at the hospital)	Furosemide was temporally stopped and then stopped completely due to another episode of hypotension.	possible
	TRAMADOL – SULPIRIDE (type C)	▪ adverse or toxic effect of other CNS depressants ▪ additive CNS-depressant effects	fall at home	Sulpiride was withdrawn at the hospital.	possible
7	LISINOPRIL – SPIRONOLACTONE – BUMETANIDE – IZOSORBIDE DINITRATE (type C)	▪ enhanced hypotensive effect ▪ altered hemodynamic status ▪ enhanced nephrotoxic effect of ACE inhibitors	hypotension, renal insufficiency (medication induced)	The diuretics, ACE inhibitor and izosorbide dinitrate were stopped. Blood pressure stayed low. Bleeding caused hypovolemia which worsened due to medication induced renal insufficiency. When bleeding stopped, blood pressure normalized.	certain
8	BUMETANIDE – FUROSEMIDE – AMILORIDE – RAMIPRIL – BISOPROLOL (type C)		hypotension at admission, declined renal function, dizziness	Ramipril was planned if needed due to protection of renal function. The combination of furosemide and amiloride was withdrawn.	possible

				Spironolactone and molsidomine were initiated lately because of congestive heart failure and edema in chronic kidney disease.	
9	LISINOPRIL – HYDROCHLOROTHIAZIDE – FUROSEMIDE (type C)		hyponatremia	Both diuretics were immediately withdrawn at the hospital.	likely
10	METOPROLOL – QUINAPRIL – HYDROCHLOROTHIAZIDE (type C)		2 falls without loss of consciousness, positive orthostatic test, hyponatremia	Hydrochlorothiazide was stopped because of hyponatremia, which was followed by a slight improvement. The daily dose of metoprolol was increased. Few days later, an orthostatic test was negative.	likely
11	LISINOPRIL – BUMETANIDE – MOLSIDOMINE (type C)		hypotension (molsidomine initiated at the hospital)	Molsidomine was stopped and blood pressure normalized.	likely
12	BUMETANIDE – SPIRONOLACTONE – LISINOPRIL – NEBIVOLOL (type C)		hypotension, bradycardia (all medications initiated at the hospital), light metabolic alkalosis due to diuretics	Lisinopril was temporally stopped for 2 days, nebivolol was withdrawn and the dose of bumetanide was increased. Hypotension and bradycardia occured again, therefore bumetanide was not administrated that day. In the next days the dose of bumetanide was slowly reduced. They tried to adjust therapy according to blood pressure.	likely
	DIGOXIN – NEBIVOLOL (type C)	▪ bradycardia	bradycardia followed by hypotension	Heart rate normalized simultaneously as antihypertensive therapy was adjusted (nebivolol was withdrawn).	possible
13	FENTANYL – HYDROCHLOROTHIAZIDE (type C)	▪ enhanced orthostatic hypotensive effect	symptoms of orthostasis (fentanyl inititated at the hospital)	During hospital stay blood pressure was rather low and was monitored.	likely
	FENTANYL – MORPHINE – LORAZEPAM (type C)	▪ adverse or toxic effect of other CNS	tiredness and disability to cooperate with	The patient was still in pain so reducing the pain medication was not	likely

		depressants ▪ additive CNS-depressant effects	medical staff (barely opened eyes)	recommended.	
14	PAROXETINE – ZOLPIDEM (type C)		3 falls at home	At the hospital the dose of zolpidem was decreased.	likely
15	LORAZEPAM – RISPERIDONE (type C)		fall at home and loss of consciousness, confusion and aggressiveness	The dosage of risperidone was increased. A physician stopped lorazepam and prescribed trazodone. Some days later alprazolam was initiated.	likely
16	ALPRAZOLAM – OXAZEPAM – CETIRIZINE (type C)		fall at home during the night, total amnesia of the fall and transport to the hospital, possible short episode of unconsciousness	At the hospital the dosages of alprazolam and oxazepam were reduced. Oxazepam and cetirizine may be taken, if necessary. Alprazolam was later changed to zolpidem.	likely
17	ALPRAZOLAM – ZOLPIDEM (type D) – ESCITALOPRAM (type C) – BETAHISTINE*		recurrent falls at home	At hospital admission alprazolam and betahistine were stopped, the dose of escitalopram was reduced and zolpidem was planned, if needed, but never administrated. Betahistine was started again few days later.	likely
18	TRIAZOLAM – LORAZEPAM (type C)		an episode of brief loss of consciousness	A physician wanted to withdrawn benzodiazepines and started an SSRI, but the patient disagreed.	possible
19	FUROSEMIDE – LISINOPRIL – BISOPROLOL – DIGOXIN (type C)	▪ enhanced hypotensive effect ▪ altered hemodynamic status	episodes of hypotension	A physician stopped bisoprolol and furosemide (bisoprolol was home medication, furosemide and lisinopril initiated at the hospital).	likely
	LISINOPRIL – BUMETANIDE – SPIRONOLACTONE (type C)	▪ enhanced nephrotoxic effect	episodes of hypotension, dizziness	Bumetanide was reduced. Blood pressure stayed rather low, therefore	likely

		of ACE inhibitors	(all 3 medications started at the hospital)	bumetanide was slowly stopped. Despite the low blood pressure, the patient was not affected anymore.	
	NADROPARIN – CLOPIDOGREL (type C)	▪ signs and symptoms of bleeding	small vaginal bleeding	A physician decreased the dose of nadroparin to preventive dose.	certain
20	RISPERIDONE – CITALOPRAM (type C)	▪ toxic effects of risperidone due to decreased metabolism caused by SSRI (e.g. weight gain, EPS, hypotension, irritability, aggression)	increased aggression and abnormal behavior at home	There have been no new episodes of confusion since risperidone was stopped. Instead of it, trazodone was administrated. Citalopram was slowly decreased and finally stopped and mirtazapine was initiated instead.	likely
21	TRAZODONE – MIRTAZAPINE (type D)	▪ serotonin syndrome (symptoms: agitation, diaphoresis, diarrhea, fever, hyper-reflexia, incoordination, myoclonus, shivering, or tremor)	episode of acute confusion with aggressiveness	Trazodone was stopped the next day. No new acute episodes of confusion occurred.	likely
	TRAMADOL – TRAZODONE – MIRTAZAPINE (type D)		EPS, agitation	Mirtazapine was initiated and the dose of tramadol was increased at the hospital. Due to an increased risk of serotonine syndrome, an intervention was made and the physician agreed to stop trazodone.	likely
22	TRAZODONE – ESCITALOPRAM (type D)		agitation (both drugs initiated at the hospital)	Trazodone was planned if needed, but it was not administered most of the time.	possible
23	AMLODIPINE, LERCANIDIPINE – LISINOPRIL (type B); AMLODIPINE – LERCANIDIPINE – MOXONIDINE – MOLSIDOMINE (type C)	▪ enhanced hypotensive effect ▪ altered hemodynamic status	hypotension (amlodipine initiated at the hospital)	Moxonidine and amlodipine were stopped and the blood pressure normalized. Blood pressure was well controlled under lercanidipine and bumetanide.	likely

	ALLOPURINOL – LISINOPRIL (type D) + CIPROFLOXACIN**	▪ lisinopril enhances the potential for allergic or hypersensitivity reactions to allopurinol ▪ enhanced nephrotoxicity	acute renal failure	Nephrotoxic medications were stopped and the patient was dialysed.	likely
24	LEVODOPA – QUETIAPINE (type D)	▪ diminished therapeutic effect of anti-Parkinson's agents	buccal dyskinesias, cogwheel rigidity	The dose of quetiapine was decreased and the dose of levodopa increased at hospital dismissal.	likely
	CLONAZEPAM – ALPRAZOLAM – FLURAZEPAM (type C) + TRAZODONE – FOSFOMYCIN***	▪ adverse or toxic effect of other CNS depressants ▪ additive CNS-depressant effects	deterioration in mental status (fosfomycin and flurazepam initiated recently)	Alprazolam, clonazepam and trazodone were withdrawn and the patient's clinical condition improved.	likely
25	INSULIN – METHYLPREDNISOLONE (type C)	▪ diminished hypoglycemic effect of antidiabetic agents	hyperglycaemia	A physician increased the dose of insulin. A few days later, episodes of hypoglycaemia occurred so they tried to optimize the dose of antidiabetic medication before the dismissal.	likely
26	DONEPEZIL – VERAPAMIL (type B)	▪ increased risk of adverse effects (e.g. bradycardia) if donepezil is given concurrently with calcium-channel blockers	bradycardia and consecutive fall	A physician decreased the dose of verapamil.	Certain

* Betahistine can cause nervous system side effects (convulsions, daytime sleepiness, confusion and hallucinations) and low blood pressure, but it does not trigger interaction in Lexi-Comp Online™.

** Ciprofloxacin is a nephrotoxic drug and iatrogenic cause of an ADE, but it does not trigger interaction in Lexi-Comp Online™.

*** Trazodone and fosfomycin do not trigger interactions in Lexi-Comp Online™, but they can cause nervous system side effects (sedation, dizziness, weakness, headache).

Table XIII DDIs responsible for an ADE, divided per drug group

*Carvedilol is a nonselective beta blocker and alpha-1 blocker.
** Zolpidem is not a benzodiazepine but acts at the same site.

[1]To get the total number of times involved it is needed to add all horizontal and vertical numbers for one drug.

	Number of times involved[1]	ACE-inhibitors	Diuretics	Beta-blockers*	Benzodiazepines**	Nitrates and other compounds that release NO	Ca-channel blockers	Opioid analgesics	Atypical antipsychotics	Miscellaneous antidepressants	Centrally acting antihypertensives	SSRIs	Centrally acting cholinesterase inhibitors	Drugs used in gout	Antibiotics	Anticoagulants	H_1-receptor antagonists	Antidysrhythmic drugs	Antiplatelet agents	Calcium salts	Corticosteroids	Dopamine receptor agonists	Insulin	LMWHs
ACE-inhibitors	28																							
Diuretics	27	14	1																					
Beta-blockers*	15	6	7																					
Benzodiazepines**	11				4																			
Nitrates and other compounds that release NO	9	3	3																					
Ca-channel blockers	8	2				2																		
Opioid analgesics	6		1		2																			
Atypical antipsychotics	5				1			1																
Miscellaneous antidepressants	5							2		2														
Centrally acting antihypertensives	4	1				1	2																	
SSRIs	4				2				1	1														
Centrally acting cholinesterase inhibitors	3			1			1		1															
Drugs used in gout	3	1																						
Antibiotics	2	1												1										
Anticoagulants	2						1							1										
H_1-receptor antagonists	2				2																			
Antidysrhythmic drugs	2			2																				
Antiplatelet agents	1																							
Calcium salts	1		1																					
Corticosteroids	1																							
Dopamine receptor agonists	1								1															
Insulin	1																				1			
LMWHs	1																		1					

7.2 RETROSPECTIVE STUDY

During the 18-months study period, 2890 alerts were generated by the CDSS (drug-drug interaction check). 2482 (85.9%) alerts were related to type 1 interactions (contraindicated medications) and 408 (14.1%) to type 2 interactions (precautionary contraindicated medications). 82.1% of all alerts were overridden. The table below shows the total number of alerts and the number of overridden alerts according to the type of intervention class and potential drug-drug interaction.

Table XIV Alerts generated by CDSS

Intervention class	Potential drug-drug interaction	Number of alerts	Percentage of overridden alerts
1	risk of hyperkalemia	2084	85.7
	risk of myopathy and renal failure	200	74.5
	risk of bleeding	147	85.7
	premature baby and infants: lung and kidney damage	18	100.0
	increased effect of rifabutin	17	52.9
	reduced efficacy of azoles	7	85.7
	increased effect of pimozide (life-threatening arrhythmias)	3	100.0
	decreased effect of beta-symapthomimetics	3	33.3
	exceptional cases of circulatory disorders and infarction	2	100.0
	antagonistic effect on the bronchi resistance	1	100.0
2	reduced cardio-protective efficacy of clopidogrel	329	64.7
	stronger adverse effects of carbamazepine/may reduce the efficacy of azoles	29	93.1
	development of serotonin syndrome	13	69.2
	increased or decreased effect of bupropion	8	100.0
	reduced or increased efficacy of voriconazole is possible	8	50.0
	increased effect of tizanidine	6	50.0
	reduced effect of opioid agonists	6	66.7
	increased effect of rosuvastatin	4	25.0
	increased effect of lercanidipine (hypotension)	2	100.0
	amantadine intoxication is possible	2	50.0
	increase in nephro-, oto- and neurotoxicity	1	100.0

7.2.1 RISK OF HYPERKALEMIA

The most common alert (N = 2084, 72.1%) was a warning for the risk of hyperkalemia. This alert was generated for 646 patients. 62.7% of alerts were generated when the patient's potassium level was too low, 36.1% when it was within the range, and 1.2% when it was too high (see Figure 7). The mean value was 3.4 mEq/L (SE = 0.66) which is below the minimum. The normal range according to the EMD is 3.6 to 5.0 mEq/L.

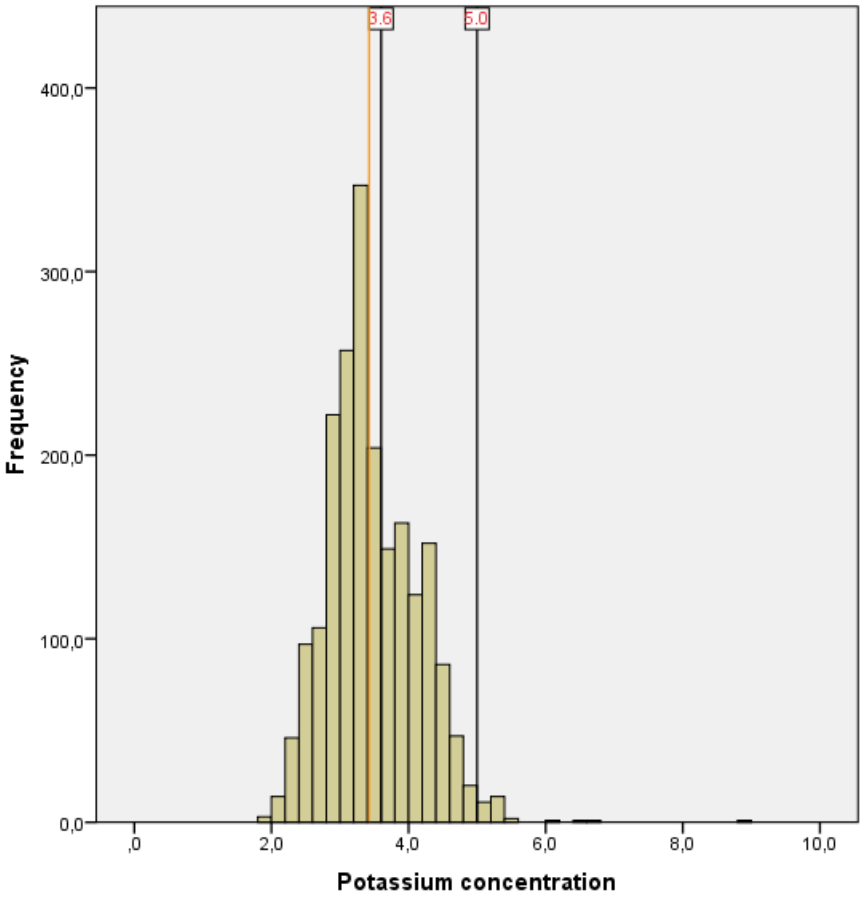

Figure 7 Frequency of alerts according to potassium concentration
(orange vertical line presents the mean potassium concentration 3.4 mEq/L, SE = 0.66, N = 2068)

In cases when the potassium level was within the range or above 5.0 mEq/L (N = 811), laboratory results for the following days were investigated. In 540 of 811 alerts (66.6%) the potassium level did not exceed the maximum value. In 81 cases (10.0%) there was no laboratory result after the date of the alert. In another 82 alerts (10.1%), the next potassium

laboratory value was at least 4 days or more after the initial alert. In 0.7% of alerts potassium lab value was above 5.0 mEq/L, but the result may be increased due to hemolyzation and therefore it was not reliable. In 1.1% of alerts, the potassium level was even too low on the date of an alert, but it went above 5.0 mEq/L in the following days. In 3.6% of alerts, the potassium level was too high on the day of the alert (in 6 cases there were no results after that date; in 11 cases the potassium level was above 5.0 mEq/L also the following days; in 12 cases the potassium level normalized in the following days). In 3.2% of alerts, the potassium level increased in the next 2 days after an alert above the upper limit of 5.0 mEq/L.

Of the alerts generated when the potassium level was below 3.6 mEq/L, 88.5% was overridden. In those alerts where the potassium level was within the range, 81.5% was overridden. When the potassium level was above 5.0 mEq/L, 80.8% of alerts were overridden (see Figure 8).

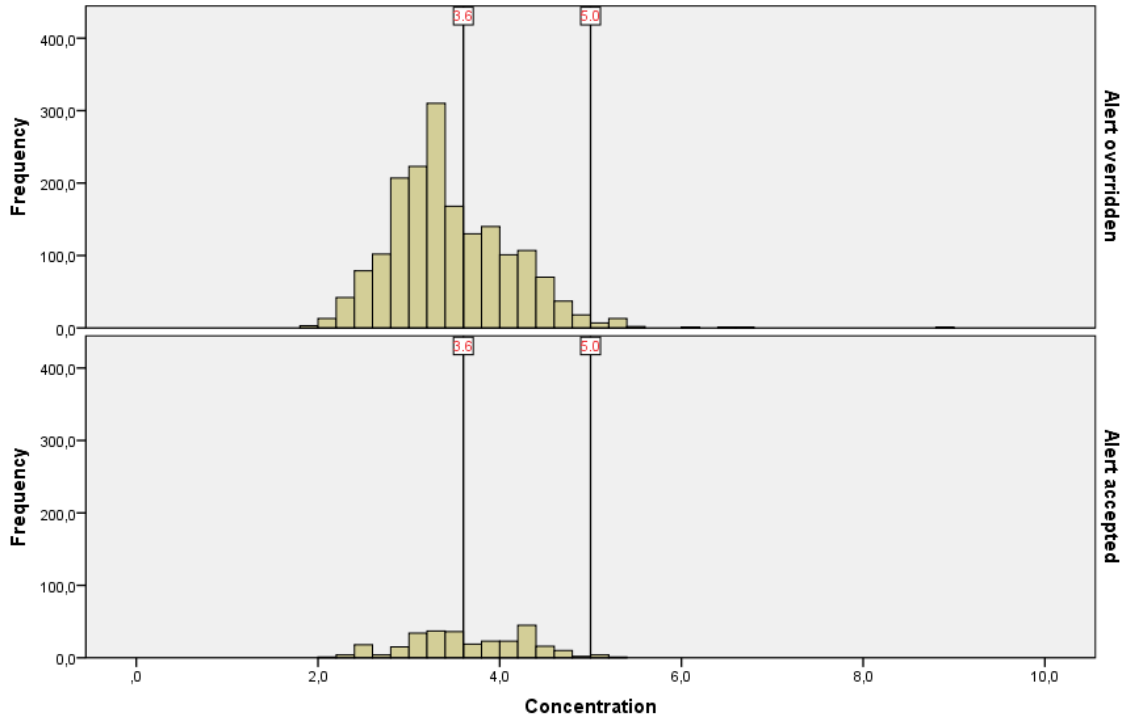

Figure 8 Frequency of overridden and accepted alerts according to potassium concentration

There was a statistically significant (p = 0.010, Pearson's Chi-Square test) relationship between the type of potassium product and the acceptance of an alert (see Figure 9). When an intravenous (i.v.) potassium supplement was involved in a drug-drug interaction alert, the alert was accepted in more cases which indicates that the physicians were aware of the fact that an i.v. supplement increases the potassium level more rapidly than an oral one. In alerts where the oral product triggered an interaction, 87.9% of alerts were overridden and in alerts which included the i.v. product, 84.0% of alerts were overridden.

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	6,628[a]	1	,010		
Continuity Correction[b]	6,307	1	,012		
Likelihood Ratio	6,671	1	,010		
Fisher's Exact Test				,011	,006
Linear-by-Linear Association	6,625	1	,010		
N of Valid Cases	2068				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 139,36.

b. Computed only for a 2x2 table

Figure 9 Chi-Square tests

			AlertAccepted		
			Alert overridden	Alert accepted	Total
ProductPotassium	CHLOROPOTASSURIL 10ML AMPUL ORAL	Count	868a	119b	987
		Expected Count	847,6	139,4	987,0
		% within ProductPotassium	87,9%	12,1%	100,0%
		% within AlertAccepted	48,9%	40,8%	47,7%
	KALIUM CHLORIDE 50MEQ/50ML VIAL I.V.	Count	908a	173b	1081
		Expected Count	928,4	152,6	1081,0
		% within ProductPotassium	84,0%	16,0%	100,0%
		% within AlertAccepted	51,1%	59,2%	52,3%
Total		Count	1776	292	2068
		Expected Count	1776,0	292,0	2068,0
		% within ProductPotassium	85,9%	14,1%	100,0%
		% within AlertAccepted	100,0%	100,0%	100,0%

Each subscript letter denotes a subset of AlertAccepted categories whose column proportions do not differ significantly from each other at the ,05 level.

Figure 10 Crosstabulation (acceptance of alert and potassium product)

An intravenous potassium supplement was involved in 43.6% of alerts when the potassium level was too low, in 67.3% of alerts when it was within the range and in 65.2% of alerts when it was too high (see Figure 10).

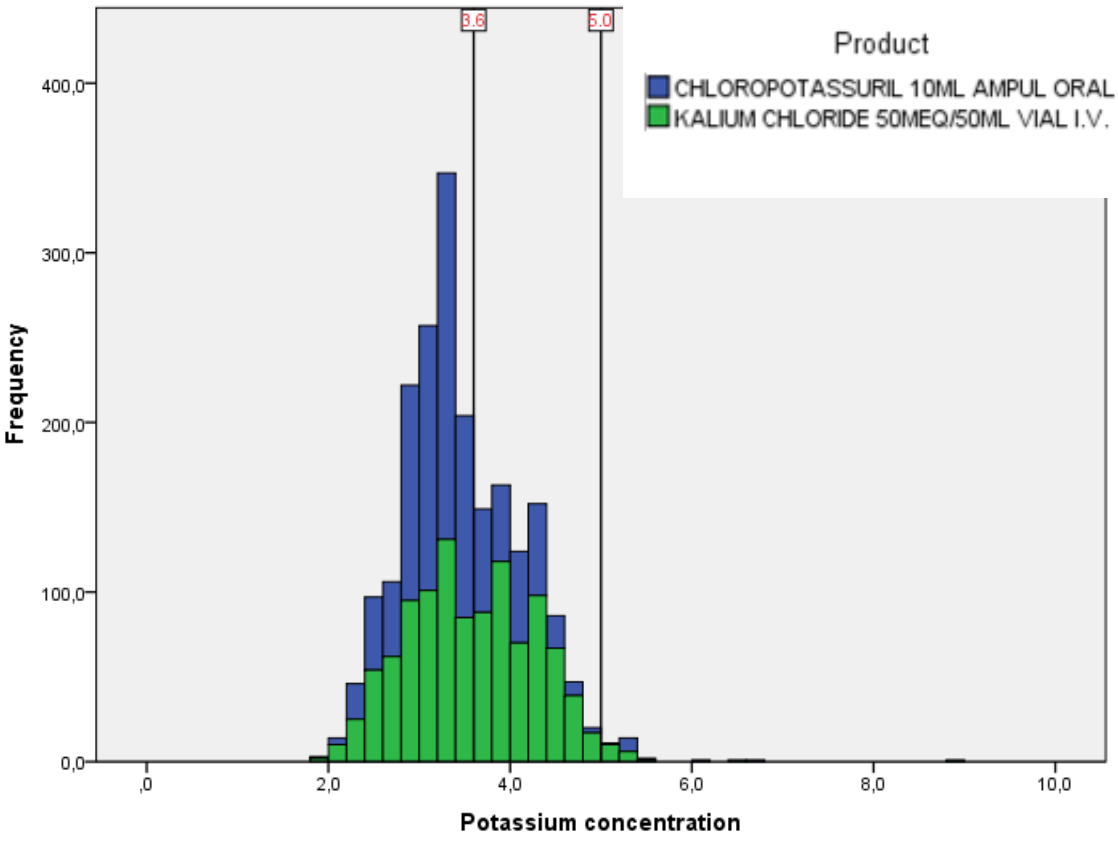

Figure 11 Oral and i.v. potassium supplements according to potassium concentration (Chloropotassuril 10ml ampul oral: mean = 3.3, SE = 0.57, N = 987; Kalium chloride 50mEq/50ml vial i.v.: mean = 3.5, SE = 0.72, N = 1081)

8 DISCUSSION

Drug-drug interactions are common in current pharmacotherapy, especially in geriatric patients, but the risks involved seem mostly acceptable. During this study many potential interactions with a high risk level were triggered. However, only a limited number of DDIs involved a risk of adverse patient outcomes. Not every interaction causes an ADE and one or more interactions can cause the same ADE although the mechanism can be different.

8.1 PROSPECTIVE STUDY

The prospective study attempted to investigate possible DDIs of type C, D and X and to identify drug combinations and patients with suspected ADE. The findings of this study are a high rate of potential DDIs and adverse outcomes due to DDIs in geriatric patients and the important role of clinical pharmacists in preventing these ADEs.

8.1.1 IDENTIFICATION OF AN ADE AND CAUSALITY ASSESSMENT

We identified ADEs mostly through electronic medical chart reviews and the detection of abnormal laboratory results. Because information may be missing in a patient's electronic medical record, the clinical pharmacists interviewed physicians and patients about the specific problems associated with their drug therapy. To eliminate concerns about the reliability of the process, we discussed all suspected ADEs with the clinical pharmacists involved in the study and 2 pharmacists (a professor in pharmaceutical care and a PhD student) of the Department of Clinical Pharmacology and Pharmacotherapy.

In assessing ADEs that occured already at home, we had some difficulties to establish whether a patient took the prescribed medicine before the event or not. It was also difficult to evaluate whether an event was related to a particular morbidity or the combination of the administered medications (e.g. mental state in elderly patients versus additive CNS depressant effect). In classifying these events we considered the timing of the findings (symptoms, abnormal laboratory results, diagnoses), whether or not the physician attributed the findings in the patient's file to the drug and if the patient himself complained about symptoms after administration of the drug.

The causality of suspected ADEs was assessed by one independent evaluator (professor in pharmacology and head of the department). However, an assessment by two or more evaluators is advisable since this would increase the reliability of the results.

An assessment of the economic savings of prevented ADEs would give useful information to the hospital administration board and would have been an important additional value to the study. However, due to time limitations this could not be performed.

8.1.2 CLINICAL PHARMACISTS' INTERVENTIONS

Because 26 patients experienced an ADE either assessed as certainly, likely or possibly caused by drug-drug interactions, the pharmacist's role in preventing them is important. Physicians were receptive to accepting suggested medication changes by pharmacists. 5 of 14 interventions included monitor advice and we were not able to verify if this advice was accepted or not. The acceptance rate of other interventions was 77.8%. 28.6% of interventions included an advice to separate the moment of intake of the interacting drugs in order to minimize the possibility of an interaction which is a simple and effective preventive measure. However, preventing ADEs caused by drug-drug interactions can only be achieved through thoroughly reviewing the medication list and the patient's file. This in turn is only possible if provided with enough time and human resources.

8.1.3 PATIENT CHARACTERISTICS

The studied geriatric population group is very vulnerable to drug-drug interactions and therefore regular medication reviews are necessary. Potential interactions of type D, where modification of therapy should be considered, often included calcium carbonate which is probably a consequence of frequently prescribed calcium supplements to older women in the context of osteoporosis. It is advised to separate the moment of intake of the calcium supplement and the interacting agent by as much time as possible and to monitor for decreased therapeutic effects of the other drug if an oral calcium salt is coadministered.

Medications most frequently prescribed in the elderly were those of the ATC group C (to treat cardiovascular diseases) and N (to treat nervous system diseases), and concomitant use of two or more of these drugs is often clinically appropriate to achieve an optimal therapeutic effect.

Consequently, drugs involved in most DDIs responsible for an ADE were ACE-inhibitors, diuretics, beta-blockers and benzodiazepines. The most common type of ADEs was falling associated with low blood pressure or with the use of psychotropic medications as well as hypotension as such. Other frequently occurring ADEs were bradycardia, dizziness, confusion, aggressiveness, loss of consciousness and renal failure caused by a disturbed electrolyte balance. These acute complications can be very dangerous and often require immediate hospitalization when they occur at home. Therefore, much attention should be given to patients with renal, hepatic and cardiac failure, which are likely comorbidities in the elderly. Blood pressure lowering agents should be initiated carefully or the doses should be adjusted to prevent adverse outcome.

8.1.4 STUDY LIMITATIONS

This study has some limitations. Due to time and human resources limitations, the interaction check was performed only on the day after the medication history was acquired by the clinical pharmacist. In 14 patients with identified ADEs, the medications involved in the drug-drug interactions related to these ADEs were not included in the DDI reports of these patients. The reason for this is that some drugs were immediately withdrawn at hospital admission, because an ADE occurred already at home. Therefore these drugs were not included in our medication list when the interaction check was performed. Also we did not check for interactions with medications prescribed after our report was made and an intervention due to new potential DDIs could not be carried out.

Although reviewing the drug therapy with one drug-drug interaction software program seemed appropriate for identifying potential drug-drug interactions, Lexi-Comp Online™ in 2 cases did not trigger DDIs responsible for an ADE. After an adverse outcome occurred, we rechecked the therapy with Stockley's Drug Interactions, which identified the causal drug-drug interactions.

A bias which is likely to occur is the impact of interventions performed by clinical pharmacists. When pharmacists suggested changes in drug therapy or gave a monitor advice, the risk of potential interactions was reduced and consequently less ADEs occurred. It would

not have been ethical, if we divided patients at the geriatric ward into a control and an intervention group and performed interventions for DDIs only in the intervention group.

Due to the time restriction and defined inclusion criteria the sample size (50 patients) was relatively small.

8.2 RETROSPECTIVE STUDY

In the retrospective study drug-drug interaction alerts for an 18-months period were analyzed. The outcomes of the study showed a very high rate of overridden alerts (82.1%), which raised questions as why did physicians override them, what effects arose and how can alerting system be improved.

8.2.1 RISK OF HYPERKALEMIA

An alert for the risk of hyperkalemia (the highest risk level) is generated when a potassium supplement and a potassium sparing diuretic are prescribed in combination. A potassium supplement is usually prescribed in order to increase the patient’s potassium level and therefore the alert is of no use and annoying if the potassium level is already too low. In 62.7% of the generated alerts the potassium level was below 3.6 mEq/L which suggests that an oral or intravenous supplement was indeed prescribed correctly. Despite this fact, it is difficult to say if the laboratory results affected the physician's decision to override an alert because of 3 limiting factors. Firstly, it was not clear if the physician had seen the lab value before he made a decision. Secondly, it is not known if at the time of prescribing the lab result was already available (there is no exact time for the occurrence of the alert and the lab result, except if there is more than 1 lab result per day). Finally, when there is more than 1 lab result on the same day, it is not known, which of them was available at the time of prescribing.

In 76.9% of alerts, the lab value was from the same day as the alert. The rest of the lab values were selected based on the nearest date to the date of the generated alert. In 110 cases the potassium level might have been increased due to hemolyzation during the measurement process which reduced the reliability of the collected results. If the potassium level was within the range or above 5.0 mEq/L, it was difficult to evaluate available results for the following days. As it is clear from the previous chapter, the results were very inhomogeneous. In 3.2%

of the alerts, the laboratory value exceeded the upper limit in the following 2 days. It cannot be interpreted straightforward that this event occurred due to the concomitant administration of a potassium supplement and a potassium sparing diuretic. Potassium levels can be affected by many factors such as the functioning of the kidneys, the blood pH, the amount of potassium you get through the food, the hormone levels in the body and severe vomiting. Moreover, potassium levels change daily.

The CDSS checks for interactions when a new drug is prescribed and takes already concomitantly given drugs and drugs given up to 3 days earlier into account. According to the high rate of overridden alerts and the low potassium laboratory values, the presumption can be made that the main drawback is the 3 days period before the date of the alert in which one of the interacting drugs can be already withdrawn (e.g. potassium supplement is given only once to improve patient's condition) so the alert has no use anymore.

It should be emphasized that only the unjustified overriding is problematic from the safety perspective. To justify the physician's decision to override an alert, each case should be investigated individually, but due to time limitations this was not possible. Clarification of the planning of both medications is additionally needed to determine if the administration of the drug combination could result in hyperkalemia.

8.2.2 STUDY LIMITATIONS

Apart from the risk of hyperkalemia, for other types of drug-drug interactions, e.g. reduced cardio-protective efficacy of clopidogrel, it was difficult to evaluate the possible consequence of an overridden alert. Therefore, only data for the risk of hyperkalemia were processed because it was unambiguously which lab parameter (potassium level) needed to be checked.

As already mentioned the main drawback of the study was not knowing the exact timing of the alerts, the drug prescriptions and the lab results. It would be useful to complete the weekly reports with an exact time of the generated alerts. It is important to mention that during the study, the IT team already added information about the timing of administration of the interacting drugs.

Another common phenomenon was observed. The CDSS generated several alerts for the same patient on the same day for the same drug combination and it was difficult to explain what the reasons were. It is possible that more than one physician wanted to prescribe the combination on the same day. Another possibility is that between 2 alerts the patient's diagnosis and laboratory results were overviewed and according to these the physician made his final decision. Further investigation of these types of alerts is recommended to find out what happened in-between.

8.3 GENERAL DISCUSSION

As the results from the retrospective study show, the rates of overridden alerts were very high. For the interaction alerts with the risk of hyperkalemia, which was the most frequent alert, only in 3.2% of all alerts (N = 811) the potassium level exceeded the upper limit in the next 2 days following an alert. This indicates that the automated systems should be altered in order to reduce the number of overridden alerts and to avoid alert fatigue.

It is also possible that relevant interactions are identified by the automated CDS system, but that currently no alert is generated, because they are not in the group with the highest risk level. A potential ADE can occur nevertheless when several DDIs of a lower risk level, but related to the same adverse outcome, are present. The identified ADEs in the prospective study were related mostly to enhanced hypotensive effects or additive CNS depressant effects. During the retrospective study period, the CDSS generated only 0.9% of alerts related to those two potential ADEs which in the prospective study occurred as most frequent. This shows that the CDSS is not designed as efficiently as it could be.

Before we act on the found potential interactions (whether they were found by an automated system or manually using a drug interaction software program), further information on the patient's medical condition and medication history is warranted when available for a detailed review.

8.4 RECOMMENDATIONS

The number of interactions can be minimized. To reduce the potential risk of an interaction, enough time and human resources should be available. It is hereby important to take into account all possible DDIs that can be related to the same adverse outcome and the start dates of the interacting drugs.

If several medicines could be causative, the non-essential medicines should be withdrawn first, preferably one at a time, and the patient should be observed during withdrawal. If a DDI is likely to be dose-related, dose reduction should be considered.

CDSS adjustment should be considered. In case of the risk of hyperkalemia, the three days period before the date of the alert turned out as too long. An automated system would become more reliable if it would check the actual administration of the medications and not only their planning. In cases when a potassium supplement is newly prescribed, the potassium level should be checked and according to it, an alert should be generated or not.

9 CONCLUSIONS

Prospective and retrospective studies showed that:

- Adverse drug events attributed to drug-drug interactions are common in geriatric patients due to polypharmacy and age-related changes in pharmacokinetics.
- Many drug-drug interactions can be avoided with a therapy review and pharmacist's intervention.
- A clinical pharmacist's intervention is an effective mean in preventing adverse drug events.
- CDSS in CPOE can be a good tool to improve patient safety but can also jeopardise patient safety if badly designed.
- Overridden alerts should be justified to prevent adverse outcomes due to drug-drug interactions and alert fatigue.

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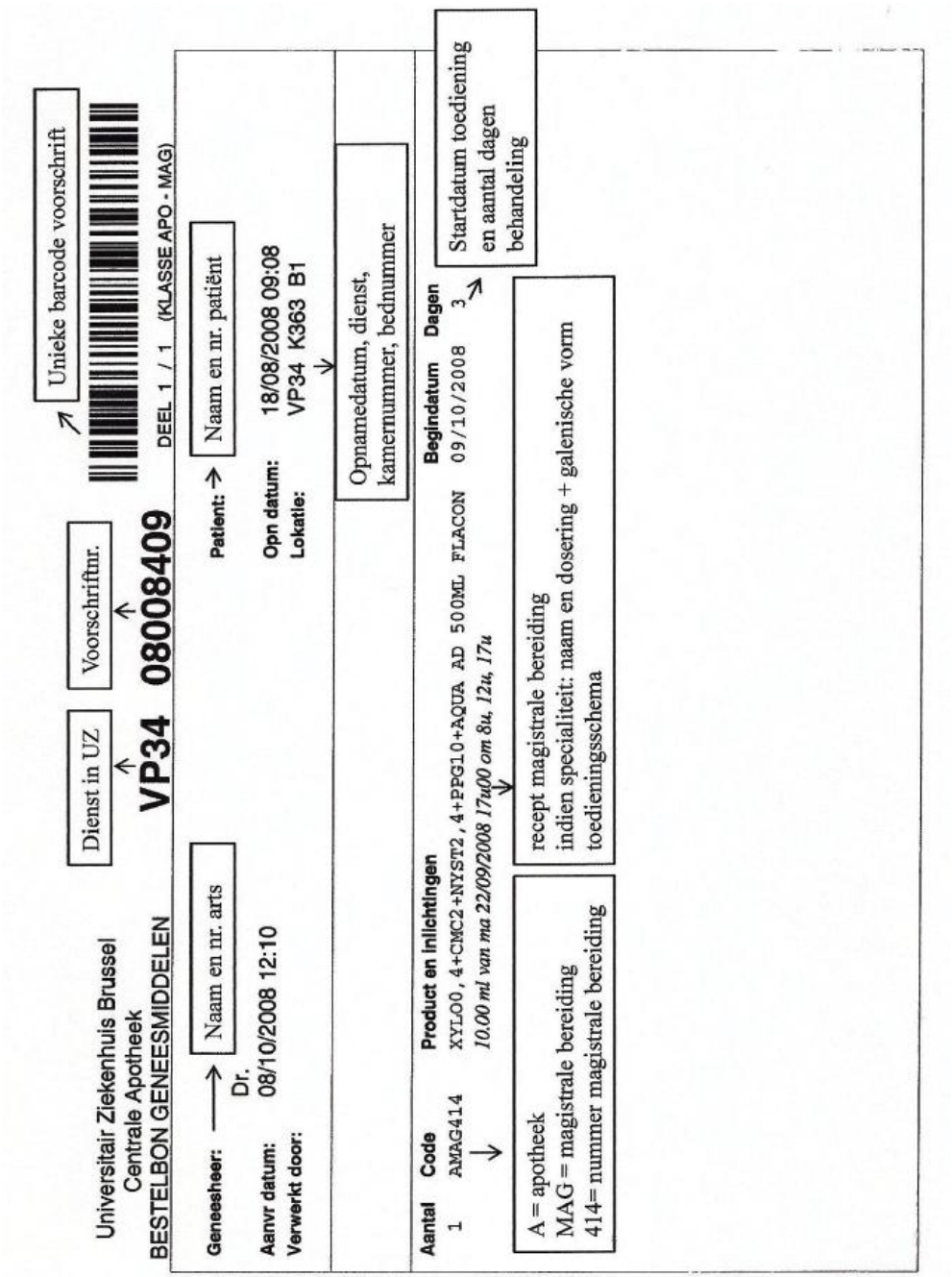
11 ATTACHMENTS

ATTACHMENT 1: ELECTRONIC PRESCRIPTION



ATTACHMENT 2: WEEKLY REPORT ABOUT DRUG-DRUG ALERTS

Periode
Mon 29/11/10 - Sun 05/12/10

Snelheid
Gemiddelde test-verwerkings-tijd (n voorschriften in 1 keer) = 931msec.
99.9% van de tests werd uitgevoerd onder de 7592msec.
95.0% van de tests werd uitgevoerd onder de 2793msec.
De maximum verwerkingstijd bedroeg 10109msec.

Aantallen
Aantal nieuwe hospitalisatie-voorschriften aangemaakt via NIEUW en OUD OE-MED-scherm tesamen (bij benadering): 6017.
Aantal nieuwe hospitalisatie-voorschriften getest via DRUG-DRUG (bij benadering): 97 % .

Interacties
41 interactiemeldingen voor 23 patiënten.
Potentiële interactie voor
Patient: [redacted]
Datum: 04-12-10
Dienst: VP33
Gebruiker: [redacted]
Interactie: Toename van de werking van de anticoagulantia - risico op bloedingen (60000035)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: SINTROM 1MG TABLET ORAL (AS02211)
Product 2: ASPEGIC 500MG VIAL I.M.I.V. (AA10601)

Potentiële interactie voor
Patient: [redacted]
Datum: 02-12-10
Dienst: EH64
Gebruiker: [redacted]
Interactie: Toename van de werking van de anticoagulantia - risico op bloedingen (60000035)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: SINTROM 1MG TABLET ORAL (AS02211)
Product 2: ASPEGIC 500MG ZAKJE ORAL (AA10611)

Potentiële interactie voor
Patient: [redacted]
Datum: 03-12-10
Dienst: VP53
Gebruiker: [redacted]
Interactie: Verminderde cardio-protectieve werkzaamheid van clopidogrel (60001162)
Interventieklasse: CONTRA_INDICATED_FOR_SAFETY
Voorgeschreven: Ja
Product 1: PLAVIX 75MG TABLET ORAL (AP07528)
Product 2: LOSEC MUPS 40MG TABLET ORAL (AL12341)

Potentiële interactie voor
Patient: [redacted]
Dienst: VP31

Gebruiker: [redacted]
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 2: ALDACTONE 25MG TABLET ORAL (AA01801)
- Datum: 29-11-10
  Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
- Datum: 03-12-10
  Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
- Datum: 03-12-10
  Product 1: CHLOROPOTASSURIL 10ML AMPUL ORAL (AC13601)

Potentiële interactie voor
Patient: [redacted]
Datum: 01-12-10
Dienst: VP33
Gebruiker: [redacted]
Interactie: Verminderde cardio-protectieve werkzaamheid van clopidogrel (60001162)
Interventieklasse: CONTRA_INDICATED_FOR_SAFETY
Voorgeschreven: Ja
Product 1: PLAVIX 75MG TABLET ORAL (AP07528)
Product 2: LOSEC MUPS 20MG TABLET ORAL (AL12301)

Potentiële interactie voor
Patient: [redacted]
Datum: 01-12-10
Dienst: EH63
Gebruiker: [redacted]
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
Product 2: ALDACTONE 25MG TABLET ORAL (AA01801)

Potentiële interactie voor
Patient: [redacted]
Datum: 02-12-10
Dienst: EH63
Gebruiker: [redacted]
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
Product 2: ALDACTONE 25MG TABLET ORAL (AA01801)

Potentiële interactie voor
Patient: [redacted]
Datum: 03-12-10
Dienst: EH63
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
Product 2: ALDACTONE 100MG TABLET ORAL (AA01803)
- Gebruiker: [redacted]
  Voorgeschreven: Ja

- Gebruiker: [redacted]
  Voorgeschreven: Nee
- Gebruiker: [redacted]
  Voorgeschreven: Nee
- Gebruiker: [redacted]
  Voorgeschreven: Ja
- Gebruiker: [redacted]
  Voorgeschreven: Ja

Potentiële interactie voor
Patient: [redacted]
Datum: 03-12-10
Dienst: EH64
Gebruiker: [redacted]
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: CHLOROPOTASSURIL 10ML AMPUL ORAL (AC13601)
Product 2: ALDACTONE 25MG TABLET ORAL (AA01801)

Potentiële interactie voor
Patient: [redacted]
Dienst: VP53
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 2: ALDACTONE 25MG TABLET ORAL (AA01801)
- Datum: 29-11-10
  Gebruiker: [redacted]
  Product 1: CHLOROPOTASSURIL 10ML AMPUL ORAL (AC13601)
- Datum: 30-11-10
  Gebruiker: [redacted]
  Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
- Datum: 30-11-10
  Gebruiker: [redacted]
  Product 1: CHLOROPOTASSURIL 10ML AMPUL ORAL (AC13601)
- Datum: 02-12-10
  Gebruiker: [redacted]
  Product 1: CHLOROPOTASSURIL 10ML AMPUL ORAL (AC13601)

Potentiële interactie voor
Patient: [redacted]
Datum: 04-12-10
Dienst: EH64
Gebruiker: [redacted]
Interactie: Toename van de werking van de anticoagulantia - risico op bloedingen (60000035)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: SINTROM 1MG TABLET ORAL (AS02211)
Product 2: ASPEGIC 500MG VIAL I.M.I.V. (AA10601)

Potentiële interactie voor
Patient: [redacted]
Dienst: VP53
Interactie: Gevaar voor hyperkaliëmie (60000112)

Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
Product 2: DYTENZIDE 50MG+25MG TABLET ORAL (AD32402)
- Datum: 03-12-10
  Gebruiker: [redacted]
- Datum: 04-12-10
  Gebruiker: [redacted]

Potentiële interactie voor
Patient: [redacted]
Datum: 01-12-10
Dienst: EH62
Gebruiker: [redacted]
Interactie: Verminderde cardio-protectieve werkzaamheid van clopidogrel (60001162)
Interventieklasse: CONTRA_INDICATED_FOR_SAFETY
Voorgeschreven: Ja
Product 1: PLAVIX 75MG TABLET ORAL (AP07528)
Product 2: OMEPRAZOLE MYLAN 20MG CAPSULE ORAL (AO12301)

Potentiële interactie voor
Patient: [redacted]
Datum: 30-11-10
Dienst: VP53
Gebruiker: [redacted]
Interactie: Toename van de effecten van rifabutine (60001037)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: MYCOBUTINE 150MG CAPSULE ORAL (AM36702)
- Product 2: KALETRA 200/50MG TABLET ORAL (AK20250)
- Product 2: KALETRA 400/100MG/5ML OPLOSSING 60ML FLACON ORAL (AK20295)
- Product 2: NORVIR 100MG CAPSULE ORAL (AN07480)

Potentiële interactie voor
Patient: [redacted]
Datum: 03-12-10
Dienst: VP53
Gebruiker: [redacted]
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
Product 2: ALDACTAZINE TABLET ORAL (AA20211)

Potentiële interactie voor
Patient: [redacted]
Dienst: VP34
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
Product 2: ALDACTAZINE TABLET ORAL (AA20211)
- Datum: 02-12-10
  Gebruiker: [redacted]
- Datum: 03-12-10

Gebruiker: [redacted]
- Datum: 03-12-10
Gebruiker: [redacted]
- Datum: 04-12-10
Gebruiker: [redacted]

Potentiële interactie voor
Patient: [redacted]
Dienst: VP53
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: CHLOROPOTASSURIL 10ML AMPUL ORAL (AC13601)
Product 2: ALDACTONE 25MG TABLET ORAL (AA01801)
- Datum: 02-12-10
Gebruiker: [redacted]
- Datum: 03-12-10
Gebruiker: [redacted]

Potentiële interactie voor
Patient: [redacted]
Datum: 29-11-10
Dienst: VP53
Gebruiker: [redacted]
Interactie: Verhoogd risico van bijwerkingen van statines - kans op myopathie en nierfalen (60000437)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: ZOCOR 20MG TABLET ORAL (AZ26001)
Product 2: BICLAR 500MG VIAL I.V. (AB04991)

Potentiële interactie voor
Patient: [redacted]
Datum: 01-12-10
Dienst: VP32
Gebruiker: [redacted]
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
Product 2: ALDACTAZINE TABLET ORAL (AA20211)

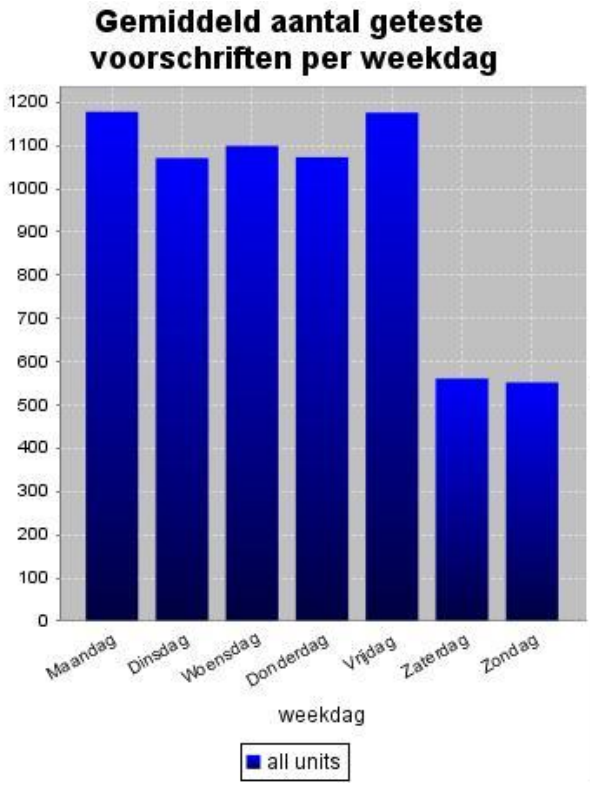
Potentiële interactie voor
Patient: [redacted]
Datum: 29-11-10
Dienst: EH63
Gebruiker: [redacted]
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Nee
Product 1: CHLOROPOTASSURIL 10ML AMPUL ORAL (AC13601)
Product 2: ALDACTONE 25MG TABLET ORAL (AA01801)

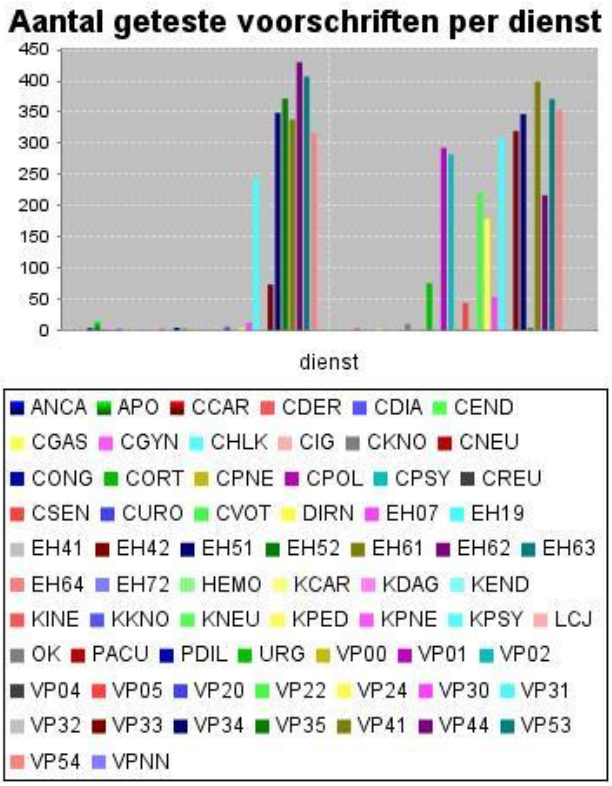
Potentiële interactie voor
Patient: [redacted]
Interactie: Gevaar voor hyperkaliëmie (60000112)

Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 2: ALDACTONE 100MG TABLET ORAL (AA01803)
- Datum: 29-11-10
  Dienst: VP41
  Gebruiker: [redacted]
  Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
- Datum: 01-12-10
  Dienst: VP44
  Gebruiker: [redacted]
  Product 1: KALIUM CHLORIDE 50MEQ/50ML VIAL I.V. (AM19511)
- Datum: 03-12-10
  Dienst: VP44
  Gebruiker: [redacted]
  Product 1: CHLOROPOTASSURIL 10ML AMPUL ORAL (AC13601)

Potentiële interactie voor
Patient: [redacted]
Datum: 03-12-10
Dienst: EH64
Gebruiker: [redacted]
Interactie: Verminderde cardio-protectieve werkzaamheid van clopidogrel (60001162)
Interventieklasse: CONTRA_INDICATED_FOR_SAFETY
Voorgeschreven: Ja
Product 1: PLAVIX 75MG TABLET ORAL (AP07528)
Product 2: OMEPRAZOLE MYLAN 20MG CAPSULE ORAL (AO12301)

Potentiële interactie voor
Patient: [redacted]
Datum: 01-12-10
Dienst: EH64
Gebruiker: [redacted]
Interactie: Gevaar voor hyperkaliëmie (60000112)
Interventieklasse: CONTRA_INDICATED
Voorgeschreven: Ja
Product 1: CHLOROPOTASSURIL 10ML AMPUL ORAL (AC13601)
Product 2: ALDACTONE 25MG TABLET ORAL (AA01801)


Gemiddeld aantal geteste voorschriften per weekdag
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
Maandag
Dinsdag
Woensdag
Donderdag
Vrijdag
Zaterdag
Zondag
weekdag
all units


Aantal geteste voorschriften per dienst
450
400
350
300
250
200
150
100
50
0
dienst
ANCA APO CCAR CDER CDIA CEND
CGAS CGYN CHLK CIG CKNO CNEU
CONG CORT CPNE CPOL CPSY CREU
CSEN CURO CVOT DIRN EH07 EH19
EH41 EH42 EH51 EH52 EH61 EH62 EH63
EH64 EH72 HEMO KCAR KDAG KEND
KINE KKNO KNEU KPED KPNE KPSY LCJ
OK PACU PDIL URG VP00 VP01 VP02
VP04 VP05 VP20 VP22 VP24 VP30 VP31
VP32 VP33 VP34 VP35 VP41 VP44 VP53
VP54 VPNN

ATTACHMENT 3: CLINICAL PHARMACIST'S INTERVENTION AS ELECTRONIC MESSAGE VIA THE EMD

ATTACHMENT 4: CLINICAL PHARMACIST'S INTERVENTION AS PAPER DOCUMENT

Universitair Ziekenhuis Brussel

Volgnummer: ... / ...

FARMACOTHERAPIECEL

APOTHEEK

FORMULIER KLINISCH APOTHEKER

Advies door

Datum:17/03/2011

- O Apr. Hilde De Ridder (dect 3264)
- O Apr. Tinne Leysen (dect 3268)
- ■ Apr. Claudine Ligneel (dect 3263)

Naam patient: [redacted]

Dossiernummer: [redacted]

Kamernummer: [redacted]

Informatie/Advies :
Graag de patiënt opvolgen voor volgende ernstige drug-drug interacties:

1. OMEPRAZOLE EG 20MG CAPS en PLAVIX 75MG:
verminderde werking van Clopidrogel door Omeprazole
Alhoewel tegenstrijdige data wordt toch aanbevolen deze combinatie te vermijden, des te meer omdat er passende alternatieven zijn voor de PPIs
voorstel is om Omeprazole te vervangen door PANTOMED 20MG of NEXIAM 20MG(pletbaar indien nodig) →OM

2. STEOVIT en EMCORETIC: Thiazidediuretica (hydrochlorothiazide in Emcoretic) kunnen de excretie van Calciumzouten doen afnemen. Case reports beschrijven hypercalcemie en tekenen van milk alkali syndroom (duizeligheid, zwakte, alkalose) wanneer tegelijkertijd thiazide diuretica en calciumsupplementen worden toegediend.
Wegens het verhoogd risico van hypercalcemie voorstel om Steovit toediening te stoppen en de calciumspiegel op te volgen →OM.

H:\APOTHEKERS\KLINISCHE FARMACIE\Interventieformulieren\INTERVENTIEFORMULIER Claudine.doc

ATTACHMENT 5: INTERACTIONS CHECK REPORT

Patient's number: [redacted]

Patient's name: [redacted]

Room number: [redacted]

Gender: F

Age: 87

Date: 01/06/2011

Hospital medications:

CIPROXINE (CIPROFLOXACINE) 500MG TABLET ORAL	ciprofloxacin
PLAVIX 75MG TABLET ORAL	clopidogrel
STEOVIT D3 1000MG/800IE KAUWTABLET ORAL	calciumcarbonaat 2,5 g + colecalciferol 800 IE
COMBIVENT AMP VOOR NEBULISATIE 2.5ML AMPUL UITWGEB	ipratropium 0,5 mg + salbutamol 2,5 mg / 2,5 ml
COVERSYL 5MG TABLET ORAL	perindopril arginine
SIMVASTATINE EG COMP PELL 1X40MG	simvastatin

- CIPROFLOXACINE (ORAL!) and CALCIUM CARBONATE, type D

Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents.

Interactions can be minimized by administering oral quinolone at least 2 hours before, or 6 hours after, the dose of an oral calcium supplement. Monitor for decreased therapeutic effects of oral quinolones if administered with oral calcium supplements.

Ciproxine and Steovit are given at the same tim (8 a.m.)!

- PERINDOPRIL and CALCIUM CARBONATE, type D

Antacids may decrease the serum concentration of ACE Inhibitors.

The US and Canadian fosinopril manufacturer labelings both recommend separating the doses of antacids and fosinopril by at least 2 hours. Ramipril systemic exposure is not affected by antacids. Recommendations regarding the administration of antacids with other angiotensin-converting enzyme (ACE)-inhibitors may vary between US and Canadian labeling and the appropriate labeling should be consulted.

Monitor for decreased therapeutic effects of ACE-inhibitors if an antacid is initiated/dose increased, or increased effects if an antacid is discontinued/dose decreased.

He was taking only cholecalciferol at home, Steovit was started at the hospital.

- SIMVASTATIN and CALCIUM CARBONATE, type C

Antacids may decrease the serum concentration of HMG-CoA Reductase Inhibitors.

Monitor for decreased effects of statins (e.g. cholesterol changes) in patients who consistently take antacids concomitantly. **This interaction is likely of little concern when antacid use is intermittent or spaced 2 hours or more after statin dosing.**

Simvastatin and Steovit are given at the same time (8 a.m.!)

ATTACHMENT 6: ATC CLASSIFICATION

CODE	CONTENTS
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Anti-infectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various