TALLINN UNIVERSITY OF TECHNOLOGY
Faculty of Information Technology

Aljona Kurbatova 182579YVEM

THE MOST FREQUENTLY OCCURRING C, D LEVEL DRUG-DRUG INTERACTIONS IN ESTONIA: PHARMACISTS IMPACT ON OCCURRING INTERACTIONS

Master's thesis

Supervisors: Kerli Metsla, MSc
Veera Bobrova, MSc

Tallinn 2020

TALLINNA TEHNIKAÜLIKOOL
Infotehnoloogia teaduskond

Aljona Kurbatova 182579YVEM

KÕIGE SAGEDAMINI ESINEVAD C JA D TASEMEGA RAVIMITE KOOSTOIMED EESTIS: APTEEKRITE TÖÖ MÕJU RAVIMITE KOOSTOIMETE HOIATUSTELE

Magistritöö

Juhendajad: Kerli Metsla, MSc
Veera Bobrova, MSc

Tallinn 2020

Author's declaration of originality

I hereby certify that I am the sole author of this thesis and this thesis has not been presented for examination or submitted for defense anywhere else. All used materials, references to the literature and work of others have been cited.

Aljona Kurbatova

20.05.2020

Abstract

The aim of the thesis was to assess drug-drug interactions (DDIs) occurred in 2016-2019 in the three months interval all around Estonia and identify top 10 C and D level DDIs. Moreover, the thesis focuses on alert system development via Estonian pharmacy professionals by their impact on interactions via computerized alert systems: their attitude towards and suggestions for improvement of existing systems. In the evaluation stage, the results were shown to the experts in the thesis topic (pharmaceutical industry) in order to find possible reasons why top 10 interactions occur more often and why they are different or similar in the particular years.

Two researches were conducted. For the quantitative research data from Estonian Health Insurance Fund were analyzed. The top 10 D and C drug-drug interactions which occurred during a three month period in September-November 2016, 2017 and 2019 were identified. Data was analyzed in MS Excel. For qualitative research were performed interviews with pharmacists and pharmacy assistants. Interviews were conducted with specialist from Ida-Virumaa, Tartumaa and Harjumaa who were selected by willingness to participate and due to different backgrounds, such as seniority, education, mother language etc. All responses of participants are kept confidential.

Results from the Estonian Health Insurance Fund show that the number of drug-drug interactions level C and D stayed comparatively on the same level through the entire investigated period. However, interactions have many similarities, they are not identical and do not stay in the same position in top 10 interactions.

Results from interviews show that the interviewees are overall satisfied with the current solution but pharmacists do not dispute with prescriber decisions. Due to that, pharmacists do not influence significantly on C and D level interactions. However, an alert system is used and patients can be notified if an interaction can be avoided, when it occurs between prescribed and non-prescribed medication.

This thesis is written in English and is 55 pages long, including 5 chapters, 10 figures and 7 tables.

Annotatsioon

Kõige sagedamini esinevad C ja D tasemega ravimite koostoimed Eestis: apteekrite töö mõju ravimite koostoimete hoiatustele.

Käesoleva töö eesmärgiks oli analüüsida Eestis aastatel 2016-2019 kolme kuu keskmisena samaaegselt väljakirjutatud ja koostoimeid omavate ravimite esinemissagedust ning identifitseerida 10 kõige sagedamini esinevad C ja D tasemega ravimite koostoimed. Samuti keskendub töö hoiatussüsteemide arendamiseks Eesti apteekrite vaatenurgast: uuriti nende suhtumist ja ettepanekuid olemasolevate süsteemide parendamiseks. Töö tulemuste interpreteerimisel konsulteeriti ka valdkonna ekspertidega (ravimitööstust), et leida erinevaid põhjused leitud tulemustele.

Töös viidi läbi kaks uurimust. Kvantitatiivseks uurimuseks analüüsiti andmeid Haigekassast. Tuvastati 10 kõige sagedamini enam väljakirjutatud D ja C tasemega ravimite koostoimet, mis esinesid kolme kuu jooksul septembris-novembris aastatel 2016, 2017 ja 2019. Andmeid analüüsiti MS Excelis. Kvalitatiivsed uuringu käigus viidi läbi intervjuud proviisorite ja farmatseutidega. Intervjueeritavad töötavad Ida-Virumaal, Tartumaal ja Harjumaal, keda valiti välja osalemisvalmiduse ja variatiivsuse tekitamiseks, näiteks tööstaaž, haridus, emakeel jne. Kogutav materjal on konfidentsiaalse iseloomuga, mistõttu vastaja ei ole tagantjärgi tuvastatav.

Haigekassast saadud andmete põhjal võib väita, et C ja D ravimite koostoimimiste koguarv püsib kogu uuritud perioodi jooksul suhteliselt samal tasemel. Kuid interaktsioonidel on palju sarnasusi, pole need identsed ega esine top 10 nimekirjas samal tasemel.

Intervjuude tulemused näitavad, et proviisorid ja farmatseudid on praeguse lahendusega üldiselt rahul, kuid apteegitöötajad ei sea kahtluse alla välja kirjutatud ravimite õigsust. Seetõttu ei mõjuta apteegitöötajad C ja D taseme koostoimete sagedust. Hoiatussüsteem on aktiivses kasutuses ja apteekrite töötajad saaksid vajadusel patsienti koostoimest teavitada ning koostoimet ennetada. Seda kasutatakse näiteks juhul kui esineb koostoime toimunud välja kirjutatud retseptiravimi ja käsimüügiravimite vahel.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 55 leheküljel, 5 peatükki, 10 joonist ja 7 tabelit.

List of abbreviations and terms

ADR	Adverse drug reaction
CDSS	Clinical decision support system
DDI	Drug-drug interaction
WHO	World Health Organization
EHIF	Estonian Health Insurance Fund
TEHIK	Health and Welfare Information Systems Centre
EMA	European Medicines Agency
FDA	Food and Drug Administration

Table of contents

List of figures

List of tables

Introduction

The drug-drug interactions (DDIs) is the effect between two or more drugs one upon another. The results of DDI are frequent, either drug might affect the person and: increase or decrease effectiveness; be neutral; or bring to adverse drug reactions (ADRs) (Brody, 2018). The clinically meaningful are DDI which can cause negative changes and bring to therapeutic failures, such as ADRs (Bucşa et al., 2012). ADR might cause patients morbidity such as bleeding or kidney damage and worst case scenario of ADR might even bring about death. (Baysari et al., 2019). Fortunately, a large proportion of ADRs are well-known and avoidable (Strandell et al., 2007). The significant DDI alerts might occur not only between prescribed medications but also with usage of non-prescribed drug combination. Moreover, drug reaction might happen with a combination of drug and food, beverage, or food supplement. Due to that, pharmacists, including pharmacists and pharmacy assistants have an alert system, which is integrated in pharmacy software's. That should help with medication dispensing/verification process (Tilson et al., 2016). That is the reason why pharmacists need a reliable DDI alert system in their everyday work life.

DDIs occur in numerous ways, including next mechanisms:

- Pharmacokinetic: Involves absorption, distribution, metabolism and excretion, all of them are linked with both treatment failure or toxicity
- Pharmacodynamics' which might be divided into three subgroups: direct effect on receptor function; interference with a biological or physiological control process; additive/opposed pharmacological effect (Palleria et al., 2013).

The Eurostat statistics in 2014 found by self-reported use of prescribed medicines in Estonia was 41.8 percent of the population (Eurostat, 2020).It is known that the more drugs are used - the higher is the risk of DDIs. The occurrence of clinically significant drug interactions is about 6% in patients taking 2–4 medications, 50% in those taking 5, and nearly 100% in those taking 10 medications (Das et al., 2019).

DDIs can happen with any patient and in any age but the main share of ADRs primarily in senior patients and patients under polypharmacy (use of 5 or more drugs) (Köhler et al.,

2000). Statistics say that DDI could account for 1% of hospitalizations in the total population and 2–5% of hospital admissions in the elderly. (Létinier et al., 2019). Moreover, DDIs also have the effect not only on hospital visits and admissions, but hospital readmission, and mortality. All those factors represent a significant burden in terms of healthcare costs and need DDIs consequences need to be prevented whenever possible (Olsen et al., 2018). In fact, doctors and pharmacists do know the most often occurring DDIs, however, it does not mean that medical specialists remember by heart all existing drugs and their side effects. Moreover, we need to admit that new drugs appear on the market regularly. That brings us to acute need of an alert system for medical workers in case of DDIs. This system helps with avoidance of medication errors while prescription and realization to the patient, whether or not there are ADR. Due to that, multiple clinical decision support systems (CDSS) - databases and screening programs have been introduced (Roblek et al., 2015). DDIs are often predictable and preventable, but their prevention and management require systematic service development by DDIs alerts systems. The pharmacists is the last official check point where patients can get warning from medical specialists before receiving medication and reduce interaction consequences for: dosage, explanation which medications, food, etc. should be avoided with concrete medication or ask about prescribed medication from doctors to ensure that no mistakes were performed. However, there is no official guidance how pharmacists should act in case of DDI. That means that decision is up to specialist.

Numerous DDI alert systems have created worldwide to aid the specialists in identifying DDIs. In Estonia a nationwide CDSS for all pharmacists has been available since 2018. There are 1106 pharmacists in Estonia and 1464 pharmacy assistants. The total amount is 2570 specialists and most of them meet DDIs daily in their work (Terviseameti registrid, 2020). This study is focusing on DDI which might happen due to usage of different medications and how pharmacists with CDSS in Estonia might influence their frequency. The pharmacists are the last official department before the patient will get medication and their input can help to understand the level of influence on DDI by pharmacists and their satisfaction of existing CDSS, suggesting possible system changes that could be made in the future. Moreover, the study is interested in how pharmacists might influence and reduce the amount of DDI. This study was also made in the interest of the Estonian Health Insurance Fund who were contacted concerning the topic of this paper.

1. Literature overview

There are numerous DDI electronic medication information systems which help medical specialists all around the globe with prevention of DDI. The literature review was conducted from a pharmacists perspective and chapter includes representation of previous researches and description of a database which is in use in Estonia in 2020.

The alerts systems mostly include interrupting alerts and non-interruptive information as forms of CDSS to warn medical workers that potential DDIs occur based on a patient's medication history.

The unwanted drug effects might happen due to several reasons, as: wrong choice of drug; failing to take account of patient liver and renal function; wrong dosage; wrong route of administration; or errors in taking the drug or transmission errors (Cascorbi, 2012).

DDI alerts most commonly occur during the prescribed medication order entry however, they might be detected by pharmacist dispensing/verification process as interactions might happen between prescription and nonprescription medication as well (Tilson et al., 2016) Because of that pharmacist might warn and sometimes prevent harm to patient caused by DDI.

Due to that monitoring for triggers by pharmacists is a very effective way to detect DDIs and explain to patients how to avoid interaction (by changing dosage of drug for example) or propose to choose alternative medication (not working for prescribed drugs).

The statistics from the World Health Organization (WHO) ADR Database (Vigibase) which contains more than 3.8 million suspected ADR reports from 82 countries reported the 35 'established and clinically important' drug pairs in those countries. The reported DDIs are shown in Table 1 where the majority of reports is related with anticonvulsants and anticoagulants but also includes statins, antineoplastic agents and antihypertensive agents (Strandell et al., 2007). Table 1 also illustrates what kind of ADR might happen with a patient, such as sepsis, vomiting, convulsions, weight increase etc.

Table 1. Clinically important drug–drug interactions due to ADR Database (Strandell et al., 2007).

Drug A	Drug B	Total DDI	Rep. after 2000	Rep. before 2000	DDI information from Stockley's Interaction Alert			Most reported ADRs
					Actions	Severity	Evidence	
Anticoagulants								
Warfarin	ASA	3956	2913	1043	Adjust	Severe	Extensive	Prothrombin decreased (661)
Warfarin	Metronidazole	300	183	117	Monitor	Severe	Study	Prothrombin decreased (92)
Warfarin	Diclofenac	281	115	166	Monitor	Severe	Case	Prothrombin decreased (25)
Anticonvulsants								
Carbamazepine	Risperidone	719	460	259	Monitor	Severe	Study	Somnolence (49)
Carbamazepine	Clozapine	422	158	264	Monitor	Severe	Case	Leucopenia (59)
Carbamazepine	Erythromycin	254	50	204	Avoid	Severe	Extensive	Drug level increased (39)
Carbamazepine	Quetiapine	253	243	11	Monitor	Moderate	Theoretical	Convulsions (22)
Carbamazepine	Ethinylestradiol	10	1	9	Adjust‡	Severe‡	Theoretical‡	†
Carbamazepine	Levonorgestrel	65	29	36	Informative	Nothing expected	Theoretical	Pregnancy unintended (22)
Phenytoin	Cimetidine	485	65	420	Monitor	Severe	Study	Rash (63)
Phenytoin	Irinotecan	40	40	0	Monitor	Moderate	Case	Convulsions (11)
Statins								
Simvastatin	Ritonavir	10	9	1	Avoid	Severe	Study	Myocardial infarction (3)
Simvastatin	Indinavir	10	7	3	Avoid	Severe	Theoretical	Myocardial infarction (3)
Simvastatin	Nelfinavir	8	7	1	Avoid	Severe	Study	Rhabdomyolysis (4)
Simvastatin	Saquinavir	3	3	0	Avoid	Severe	Theoretical	†
Simvastatin	Tipranavir	1	1	0	NA*	NA*	NA*	†
Antineoplastic agents								
Methotrexate	Probenecid	7	6	1	Adjust	Severe	Study	Sepsis (3)
Ciclosporin	Idarubicin	6	4	2	Adjust	Severe	Study	Thrombocytopenia (2)
Irinotecan	Phenobarbital	8	8	0	Informative	Unknown	Theoretical	Sepsis (4)
Irinotecan	Primidone	1	1	0	NA*	NA*	NA*	†
Irinotecan	Carbamazepine	14	11	3	NA*	NA*	NA*	Vomiting (5)
Busulfan	Metronidazole	13	12	1	NA*	NA*	NA*	Bilirubinaemia (5)
Antihypertensive agents								
Propranolol	Chlorpromazine	166	42	124	Informative	Moderate	Theoretical	Hypotension (11)
Diltiazem	Midazolam	99	44	55	Monitor	Severe	Study	Hypotension (20)
Others								
Insulin	Rosiglitazone	857	857	0	Avoid	Severe	Study	Weight increase (165)
Paroxetine	Venlafaxine	567	431	136	Monitor	Severe	Case	Suicide attempt (83)
Cimetidine	Theophylline	466	46	420	Adjust	Severe	Extensive	Drug level increased (81)
Aminophylline	Cimetidine	162	13	149	Monitor	Severe	Study	Death (13)
Erythromycin	Verapamil	152	33	119	Monitor	Severe	Case	Nausea (13)
Clomipramine	Fluvoxamine	138	77	61	Adjust	Moderate	Study	Drug level increased (16)
Diazepam	Rifampicin	74	24	50	Monitor	Moderate	Study	Hepatitis (9)

Summary of reporting of clinically important drug–drug interactions (DDIs) in the WHO-ADR database grouped by major therapeutic areas. *NA, No information available. †Several different ADR *terms* were recorded in this/these reports, but only one occurrence of each term. ‡Referring to combined hormonal contraceptives. Study = Information based on formal study [5]. Case = Information based either on a single case report or a limited number of case reports [5]. Theoretical = Information based on a theoretical interaction or lack of interaction [5].

.

However, the alert system has a positive impact on the prevention of DDI negative effects, even if there is frustration and dissatisfaction for DDI alerts by some users. Studies show that clinicians might override 49%–96% of drug alerts and due to that do not read the majority of alerts presented because they classify some alerts as not serious or irrelevant. That might happen due to drugs which were prescribed but the patient decided not to use them or if medication is bought for the patient and other persons (family members for example) at the same time. Because of that software default setting, alert fatigue may happen and users might ignore alerts, feel overwhelmed and desensitized to alert presentation. (Tilson et al., 2016).

Information content should be regularly improved towards:

- Alerts should not unnecessarily disrupt workflow,
- Information should be safe and efficient. (Sijs et al., 2006).

A review by Indermitte et al. focuses on the DDI alert system in Switzerland. Results showed that the alert system accomplished the main goal and discovered severe drug interaction (all cases caused an intervention) although the above-described problem does exist. The research involved 600 patients (with 2 or more prescribed drugs) and the pharmacists were interviewed about their management of DDIs alerts. In the study 15 pharmacies participated and the results show that and from them: in the four the computer systems were programmed to flag only 'severe' DDIS; in the six 'severe or moderate' and ‘severe, moderate or minor' in the five pharmacies. The median frequency of drug-interaction alerts increased with decreasing default severity level from 0.5 to 40, accordingly, to 76 per 40 patient visits and pharmacy. Because of these default settings, 2% of potential DDIs alerts on new or repeated prescriptions were overridden by the computer systems. Only 5% of potential DDIs emerged from new prescriptions. From the systems produced alerts, 22% were insignificant due to repeated alerting of the same DDI conjunction currently no longer taken. Of the appropriate DDI alerts 7% were overridden by community pharmacists without any action taken. If the pharmacist took care of a patient's prescription personally (as opposed to just controlling a prescription after a technician took care of the patient), fewer DDIs alerts were overridden by the pharmacist. Technical overrides (by default settings) and pharmacists' overrides together accounted for 9%. Of the remaining interactions alerts, 2% were checked more

closely by consulting the literature, contacting the prescribing physician or considered with the patient. This led to 2% interventions (close monitoring, adjustment of dose or ingestion time, therapy stop or switching to alternative therapy) (Indermitte et al., 2007).

1.1 INXBASE-RISKBASE (SFINX-PHARAO) database overview

SFINX database and web application PHARAO is in use in Estonia from June 2016 for physicians. The systems are represented by OÜ Celsius Data and funded by Estonian Health Insurance Fund (EHIF) for five years. After five years the contract will be extended assures EHIF. The full service (funded by EHIF) is available only for the physicians. For the pharmacies, DDI alerts only between prescription drug and non-prescription drug. Pharmacies, who are using the service to identify the interactions between two prescription drugs, have bought the license by themselves and from 2018 database is in use by most of the Estonian pharmacy specialists. The database of DDIs SFINX (Swedish, Finnish, INteraction X-referencing) and web-based application and PHARAO (Pharmacological Risk Assessment On-line) has been created in a collaboration between Karolinska Institute's department for clinical pharmacology in Huddinge, Sweden, the Department of Drug Management and Informatics of Stockholm County Council and Medbase Ltd in Turku, Finland – a spin-off company from the local university's clinical pharmacology department (Medbase, 2017). The SFINX is updated four times a year. In the 2017 the name of the SFINX interaction database was changed to INXBASE and the name of PHARAO to RISKBASE due to international reasons (Duodecim Terveysportti, 2017).

The web-based application is the basic tool to handle DDIs for physicians, pharmacists and nurses. It contains short, and concise evidence-based information concerning consequences of and recommendations for DDIs (Multirec, 2020). In INXBASE - RISKBASE is registered around 2,717 active substances and 19,086 combined effects. The database contains information about relevant pharmacokinetic interactions, which are supported by scientific literature or by clinical studies (approved by EMA and/or FDA). INXBASE also covers herbal preparation, minerals and drug-food interactions that can cause the most common interactions. The database does not identify custom-made medicine (handmade). The INXBASE has been in daily clinical use for more than a decade and this database being the most used software in Scandinavia for evaluating the DDIs (Eesti Haigekassa, 2018).

Interaction texts are based on substance names and on substance formulations. The alerts are divided according to clinical significance (A-D) and documentation level (0-4), which enables automated warnings. The automatic warnings occur for clinically significant interactions and are displayed with „warning“: D (red) interactions and C (yellow). The system is explained in Table 2. (Multirec, 2020).

Table 2. Classification categories in INXBASE for clinical relevance (A-D) and level of documentation (0-4), derived from an earlier Swedish interaction classification system by Sjöqvist.

Classification	Definition
A	Minor interaction of no clinical relevance.
B	Clinical outcome of the interaction is uncertain and/or may vary.
C	Clinically relevant interaction that can be handled e.g. by dose adjustments.
D	Clinically relevant interaction. The combination is best avoided.
0	Data derived from extrapolation on the basis of studies with similar drugs.
1	Data derived from incomplete case reports and/or *in vitro* studies.
2	Data derived from well-documented case reports
3	Data derived from studies among healthy volunteers and/or pilot studies among patients.
4	Data derived from controlled studies in relevant patient populations

The proportion interaction shows that C group occurs more often (i.e. combinations that are not contraindicated, but that may be of clinical consequences): A - 6 %; B - 28%; C - 50% and D-16%.

The information is evaluated and interaction texts are divided into five different parts: medical consequence, recommendation, mechanism, backgrounds and references (Böttiger et al., 2008).

1.1.1 Estonia pharmacy software

The various medical workers have different software’s, where DDI alert system is in use. For instance, family physicians use: Pereast 2; Watson, Arstiportaal +, Medicum family physicians’ softwares.

The same is for the pharmacists. In Estonia three pharmacy infosystems exist:

- Noom (OÜ Apteekide Infotehnoloogia)
- Hansasoft (Hansasoft OÜ)
- Mini Information System Portal (MISP).

All solutions are a web-based services. Users are authorized based on their IP address. When selling a digital prescription, a request is made in the background to the Prescription Center of the EHIF. All prescriptions valid at the time of the inquiry related to a specific personal identification code and prescriptions. If there is an interaction between medicines, a message will appear in the pharmacy information system (*Hansasofti apteegi infosüsteemi…*)

Each case should be approached on an individual basis and pharmacists need to decide which actions need to be done. (*Hansasofti apteegi infosüsteemi…*). For example, if DDI is between non-prescribed and prescribed medication when pharmacists might advise to choose an alternative drug. In case of DDI between prescribed drugs the pharmacist might advise patient ask to review the treatment regimen for side effects at the next doctor's visit.

The interaction check starts automatically when the payment procedure is started after adding them to the shopping cart. If the system finds an interaction in the active shopping cart or in an active and previous purchase by the same person, a window will appear on the screen showing the number of interactions and information about the interaction. The classification of the interaction, the level of documentation, the active substances present in the interaction, the clinical consequence, a link to additional information and the medicines with the interaction with the dates of purchase are displayed. The interaction warning is informative and does not interfere with the purchase process (*Hansasofti apteegi infosüsteemi…*).

The databases contain both prescription and over-the-counter medicines, as well as the most common herbal preparations. Interactions are based on the active substance registered in the database, in addition to the pharmaceutical form. The users will notice only C and D interaction which can be view on the Figure 1-5 in different solutions (Hansasoft, Noom and MISP).

1.1.2 Noom

NOOM Pharmacy software is used in over 300 pharmacies in Estonia, including the chains such as Apotheka, Koduapteek, Terve Pere Apteek and Farmacia (Astro Baltics, 2020).

In 2020 is in use version 2.0. If there is a DDI between the prescribed medications, then a red exclamation mark will be displayed (view figure 1). However, if there is potential interaction with food or supplements then yellow exclamation mark will be shown. (*Koostoimete kontroll tarkvaras…*)

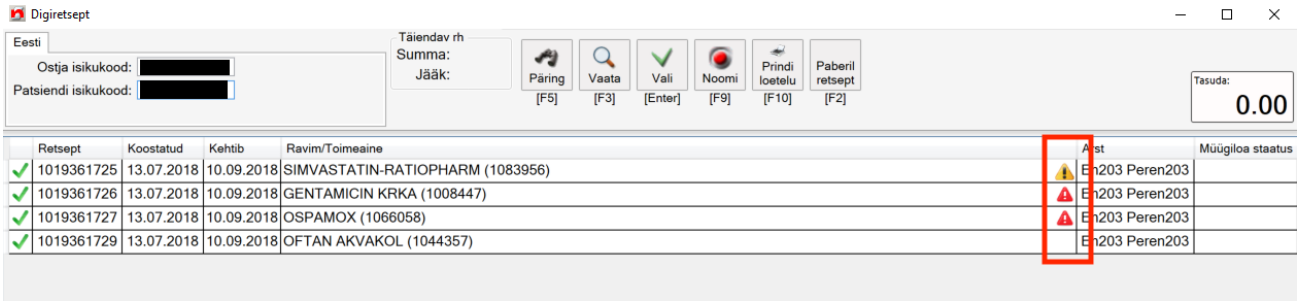


Figure 1. DDI alert in the Noom.

For more information about the interaction can be obtained by pressing the exclamation mark. If the DDI is related to a specific prescribed drug then it is displayed in reference (figure 2). (*Koostoimete kontroll tarkvaras…*).

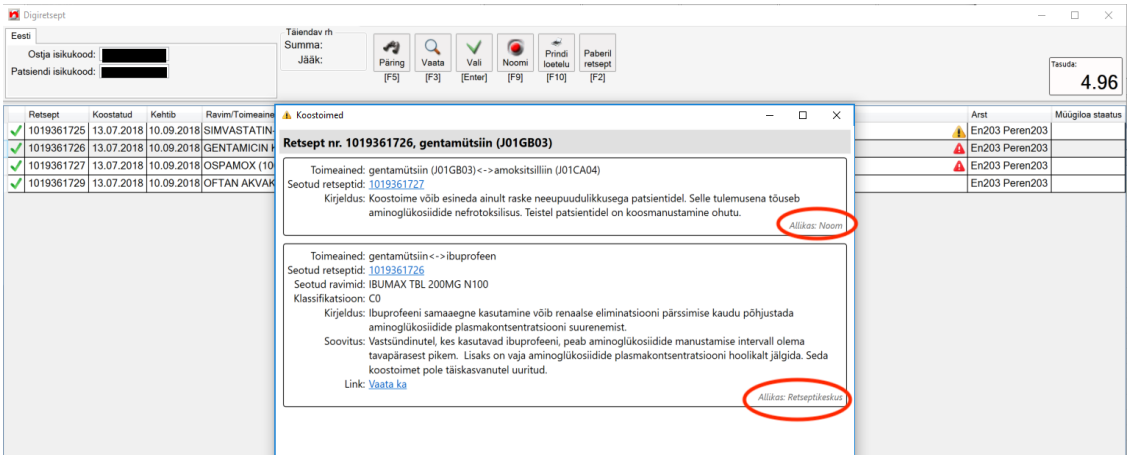


Figure 2. DDI between Gentamicin and Ibuprofen (C0) in Noom

DDI could be checked in the sales window according to the selected settings: automatically or by the user. For automatic DDI check, must be switched on automatic interaction check

(figure 3). If automatic checking is turned off, the user can check the DDI of the products in the shopping cart at any time (*Koostoimete kontroll tarkvaras…*).

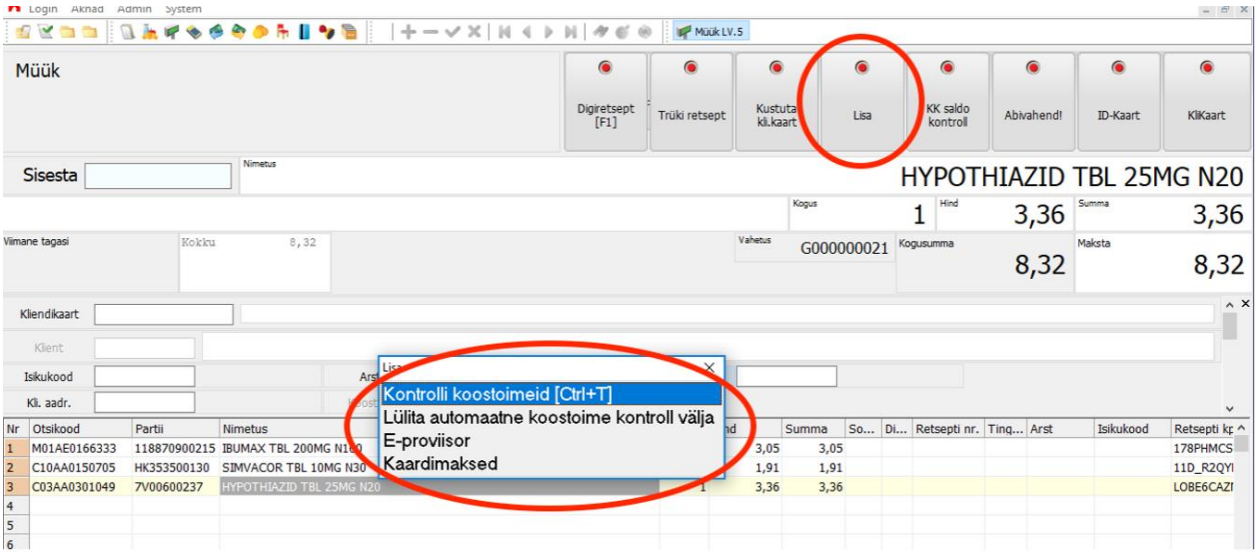


Figure 3. Alert system in the Noom.

1.1.3 Hansasoft

Hansasoft users are the next corporations: Apteek 1, Benu Apteek, Ülikooli Apteek, and Euro Apteek. Figure 4 shows how D interactions look like for users on the example of Warfarin and Ibuprofen.

Figure 4. DDI between Warfarin and Ibuprofen (D4) in Hansasoft

1.1.4 MISP

MISP was developed by TEHIK (Health and Welfare Information Systems Centre) in order to make it possible to use the service online in case of no local information system. Due to that the number of users is minimal by comparing with Hansasoft or Noom. In Estonia are registered 11 legal entities and are around 20 pharmacies in total. The DDI in MISP looks like Figure 5.

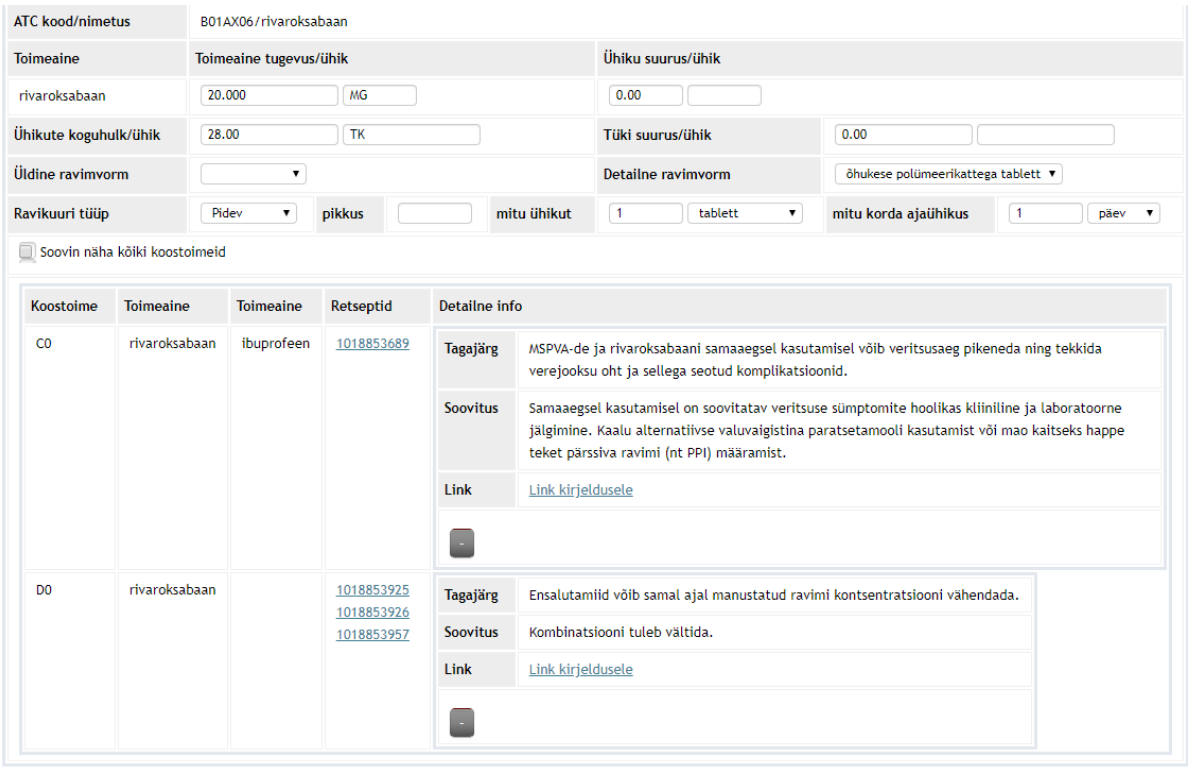


Figure 5. DDI between Rivaroxaban and Ibuprofen (C0) in MISP.

1.2 Aim of the research

The aim of the thesis was to assess DDIs occurring in 2016-2019 in the three months interval (September-November) in Estonia and identify top 10 C and D level DDIs. The time interval and duration in the present study was chosen by the author. The further aim was to see the effect of pharmacists and pharmacy assistants work to the outcomes by their impact on interactions via computerized alert systems: their attitude towards and suggestions for improvement of existing systems. For more in depth understanding of the interactions and the possible causes experts in the field were contacted to find possible reasons why top 10 interactions occur more often and why are they different or similar in the particular years and do pharmacists might influence on DDI frequency.

1.3 Hypotheses

1. Top 10 DDIs are the same in different years (2016-2019) and frequency of interactions stays on the same level.
2. Pharmacists' accession in 2018 did not decrease the amount of DDIs.

2. Method and materials

Two research were performed to test set hypotheses. For approval or disapproval of hypothesis were conducted two researches: quantitative and qualitative.

For quantitative results were analysed DDIs with level C and D, which occurred in a three month period. Data was given by EHIF. For qualitative research ten pharmacy specialists, as pharmacist and pharmacy assistants were interviewed. Interviewees gave spoken consent before interviewing.

The results were shown to the filed experts (pharmacy), with regard to the topic. The purpose was to get an expert view on possible results reasons.

The permission of the ethical committee was not asked due to usage of information, which did not contain patients' nor pharmacists personal information. Moreover, the results from interviewed pharmacy specialists in the research would not contain any information that could be used to identify them.

2.1 E-prescription data

For quantitative results data was asked from Estonia Health Insurance Fund. The aim was to find out how much C and D level interactions happened in the period September-November 2016, 2017, 2018 and 2019. Date period of comparison was three months (September-November) of DDIs, which was happening in Estonia. The time interval in the present study was chosen due to integration of alert system in the summer 2016 for medical specialists such as family physicians in Estonia. That means that data from autumn 2016 will show interactions, which happened when the alert system was already integrated for doctors. The time interval duration should be both long enough to find the most often occurring DDI and short enough to exclude for excessive data processing and the three month period is relevant due to the author's viewpoint. Unfortunately, the 2018 data was lost by EHIF and could not be restored fast enough for this study analysis.

Based on the data which were supplied from EHIF, analysis was performed. The study focuses on the number of all displayed interactions between all recipes in a specified period of time.

From the received data were possible to investigate:

- How many DDI happened in 2016, 2017, 2019 in a three month period?
- What are the top 10 DDI pairs C and D level during the study period?
- Are the top 10 DDI are the same in 2016, 2017, and 2019?
- How many times drugs with DDI were cancelled?
- Are there changes in interactions in 2019 due to pharmacists' and pharmacy assistants accession to database in 2018?

After data analysis the results were presented to experts in the pharmacy field to get comments regarding occurred DDIs and possible reasons.

2.2 Interviews

An interview was chosen due to its effectiveness to gather valuable insights because it is a more flexible and far more personal type of investigation. The interviewer might have a better understanding of the participants' attitude for the DDI topic. For instance, Phellas et al. describes that interviews have specific advantages over questionnaires. It gives the possibility to ask for clarification if the participant does not understand the question or if the putted question gets too brief an answer which does not answer the question fully. Moreover, follow-up questions can be asked to evoke a more thorough response. It leads to more detailed and thorough data in comparison with written questionnaire. In general, being asked questions by an engaged listener is experienced as more valuable by respondents than filling in a form for some anonymous researcher, so it is mostly found that less people deny to take part and more questions can be asked of each respondent (Phellas et al., 2011).

The interviews were conducted with Estonian pharmacists and pharmacy assistants. The main goal of interviews were to analyze how pharmacy specialists influence DDIs frequency and what is the level of satisfaction with current solutions (as NOOM, Hansasoft, and MISP). Moreover, the aim of interviews was to find out how a system might be developed. For that

purpose a standardized structured questionnaire was developed in a set manner: the same questions were asked in specific order, to ensure no variation between respondents' interviews.

The interview questions were mostly based on existing questionnaire by Kwak et al. The aim of study was to reveal the perspectives of non-pharmacy professionals regarding the development of pharmacist-involved medication management in long-term care facilities. However, even if topic is remote to this thesis aim, the template on this study could and was modified. (Kwak et al, 2019).

Respondents' answers were recorded and decoded after in writing form. Participants were aware that their answers are recorded and gave consent. However, the interview assumes anonymity and due to that the names, surnames of participants, as well as certain pharmacy locations are unspecified in this thesis. That was done to ensure the likelihood of giving more honest answers. The interview guide was created in three languages and is added In English (appendix 1), Russian (appendix 2) and Estonian (appendix 3).

Interviews were planned to be done face-to-face. However, because of the COVID-19 outbreak, it was decided not to conduct further planned interviews face-to-face and perform them in a healthy and safe way. Due to that, online in real-time videoconferencing or audio conferencing, using Facebook messenger, Viber and Skype was chosen.

3. Results

The data from EHIF was received electronically, via email in Excel format. The data analysis was also done in MS Excel.

The interviews were voice recorded and analyzed using Microsoft Word and in MS Excel to create graphical representation of data.

3.1 Result from E-prescription database

Data included a comparison of drugs, which had DDIs from September-November 2016, 2017 and 2019 based on their date of issue.

Firstly, the total number of prescriptions, which happened in Estonia in the above-stated period of time in 2016, 2017 and 2019 were defined. As it is seen on table 3, the C and D DDI alerts stay basically on the same level and average in percent are 31, 4 % (33,1 % in 2016, 31,5% in 2017 and 29,7% in 2019). The expert in the field pointed out that there seems to be a small but constant change in the decrease direction and it worth noting (for example 2016 vs. 2019 is a decrease of 3,4%).

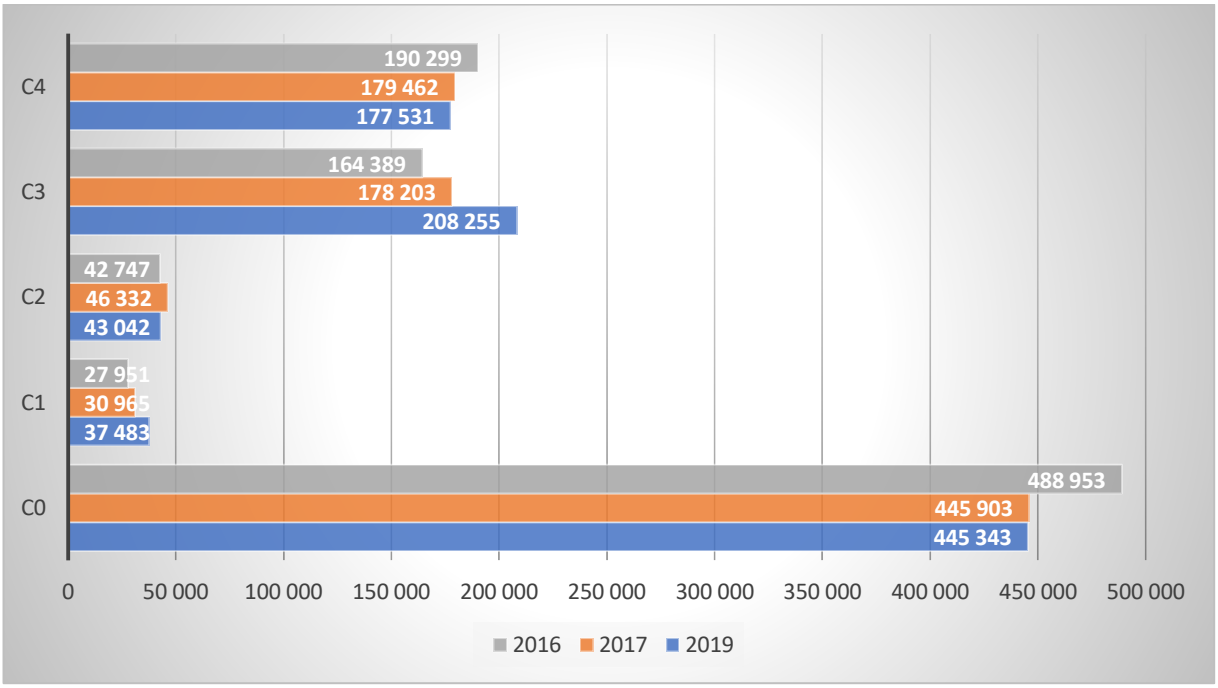
Moreover, table 3 shows that there are cancellations for drugs, which had DDIs, however, the percentage of those is extremely small and data shows that cancellation stays on the same level in all examined years around 0,1%.

Table 3. General information about DDI in 2016, 2017, 2019.

Date	**Total number of prescriptions**		**The Number DDIs with level C and D**		**Cancellation due to DDI**	
01.09.2016-30.11.2016	3,099,961	100%	1,026,941	33, 1 %	3,107	0,1%
01.09.2017-30.11.2017	3,158,709	100%	994,237	31,5%	3,011	0,1%
01.09.2019-30.11.2019	3,368,741	100%	1,001,309	29, 7%	3,514	0,1%

Further, let's look separately on C and D level interactions. The results of the C level interactions might be seen in figure 6. The table shows that the most often occurring C interaction is C0 in all analyzed years.

Figure 6.The number of C level alerts DDI in 2016, 2017 and 2019.



Also, results show that there is a positive small decrease in C0 and C4 even if the amount of interactions stays more or less on the same level. Furthermore, the most often appearing interactions by level in comparison, vary by years. For example, the most interactions between analyzed years in groups C4 and C0 occurred in 2016, C3 and C1 had more DDI in 2019 and C2 level in 2017.

One of the consulted experts pointed out that C4 is certainly the most important level in the C group. The DDI results, which are based on controlled clinical trials, lead to the fact that the number of C4 warnings has decreased by 6,7 % (by comparison 2016 results with 2019). That could be identified as a positive indicator.

The same analysis was performed for D level interactions. Results can be found in the figure 7. The numbers shows that in comparison with C, D level interactions is less frequent. In the three years occurred 2,028,250 DDIs (level C and D), where 1,825,933(around 90%) was C level and 89,655 were D level (10 %).

The results per each group (D0-D4) is not so homogeneous, as it was with DDI level C. For example, D4 and D3 show, that amount of DDI in 2019 is less almost in a half in comparison with 2016 and 2017. Moreover, there results show that the most often happened interaction in comparison in years happened in level D4, D3, D2 and D1 was in 2016. However, in 2019 D0 had more DDIs than in 2016 or 2017.

According to the expert opinion the results show a significant decrease in D4 and D3 in 2019, by 53,3% (in comparison of 2016) and 41,7%, (in comparison with 2017). Group D are clinically relevant interactions, so such a large change can be considered as significant and positive.

Figure 7. D level DDI in 2016, 2017 and 2019.

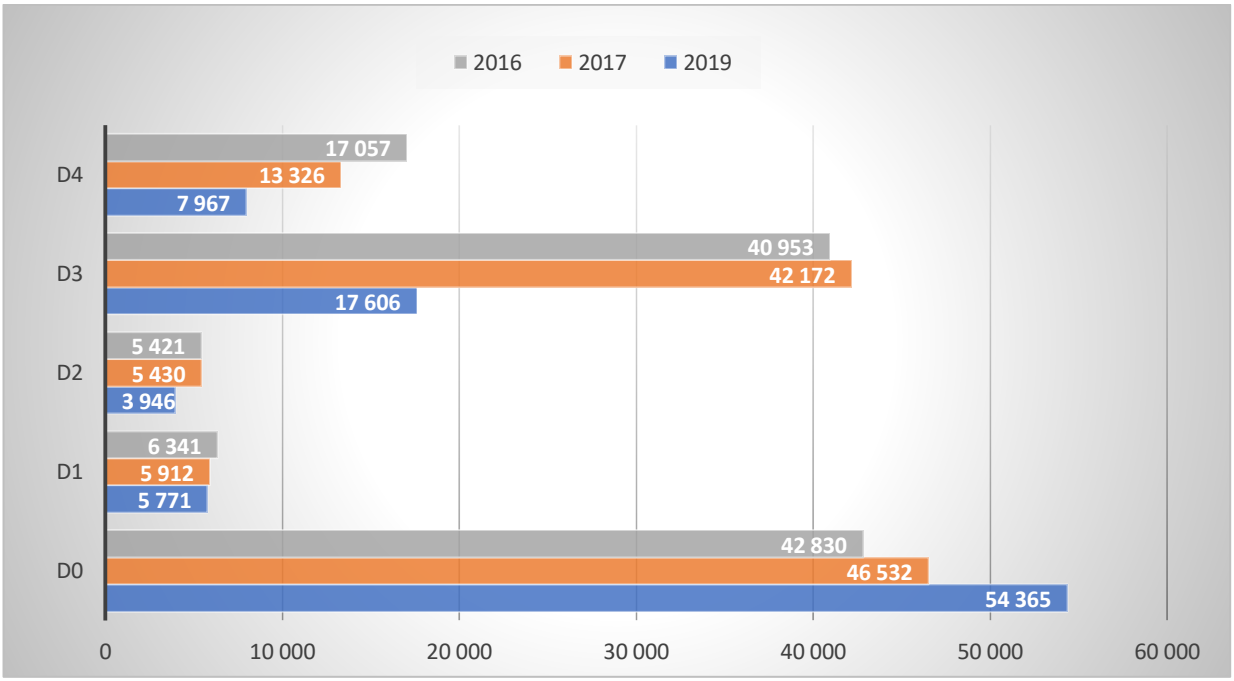


Table 4. Number of people who had D level alerts of DDI in 2016, 2017 and 2019.

DDI level clarification	**2016**	**2017**	**2019**
C0	57 671	53 523	51 118
C1	5 618	5 837	6 151
C2	6 845	6 975	6 392
C3	25 909	27 379	29 836
C4	31 437	28 973	26 750
C total	127 480	122 687	120 247
D0	9 131	9 296	11 149
D1	1 200	1 094	981
D2	1 383	1 330	1 020
D3	6 270	6 166	3 285
D4	3,456	2 622	1 497
D total	21 440	20 508	17 932
Total	148 920	143 195	138 179

Table 4 shows the same data, from the perspective of how much patients had DDI total and per each group. Due to that information can be said the average number of prescriptions, who had significant DDI (C and D) in analyzed years is around 7. Moreover, the amount of the patients, who had D4 and D3 in 2019 confirms positive trend, which prove decrease of DDI in this groups.

The data analysis identified the top 10 most often occurred DDI, level C and D in 2016, 2017, and 2019. The results can be viewed on the table 6 and 7. The tables also show level and how much interaction happened in specific year. The same interaction combinations in different years were assigned with the same color for better perception. The combinations, which do not have colored backgrounds do not overlap with results of other years.

The results show that DDIs in 2016 and 2017 have more matches with each other than DDI 2019. Moreover, some combinations changed their groups. For instance, the most often C level combination in 2019 is Metoprolol & Propafenone, however, the same pair was

classified as D level in 2016 and 2017. That means that Metoprolol & Propafenone combination is stable in use, however, risk of interaction is now rated differently (D> C).

The DDIs were grouped into categories and they are presented in table 5. Furthermore, categories are added to table 6 and 7 and can be found after each drug pair in the parentheses.

Table 5 . Related disease categories regarding top 10 DDIs.

Related disease category	**Explanation**
1	Anticoagulants and NSAID (Non-steroidal anti-inflammatory drugs)
2	Congestive heart failure and Antihypertensive drugs
3	Medications related to Psychiatric diseases
4	Drug for nervous system and cardiovascular diseases
5	Pain relief and Nervous system diseases
6	Cardiovascular diseases
7	Cardiovascular diseases and anticoagulants
8	Digestive system diseases and Thyroid hormone

The experts pointed out Warfarin should be replaced by more recent drugs with less side effects. However, combinations as Diclofenac & Warfarin, Rivaroxaban & Warfarin and others still can be found in the top most often occurring DDIs. The reason why this combinations are displayed may happen due to several reasons. For example, doctor do not cancel old prescriptions, or cannot cancel because the prescription is done by another doctor. If prescription is canceled, it is not taken into account in the DDI calculation. However, if a patient bought a prescribed drug, it is taken into DDI calculation statistics. In this case, alert system will show significant DDI, patient need to be warned and avoid Warfarin usage with new prescribed drug. Due to that, EHIF plans to allow doctors cancel prescriptions by another doctor and do so to reduce the amount of false DDIs.

Table 6. Top 10 interactions in significance level C.

	Drug pair in 2016			Drug pair in 2017			Drug pair in 2019		
1	Diclofenac & Metoprolol (1)	C0	**41,058**	Diclofenac & Metoprolol (1)	C0	**23,285**	Metoprolol & Propafenone (2)	C3	**23,024**
2	Warfarin & Torasemide (7)	C2	**16,011**	Warfarin & Torasemide (7)	C2	**16,190**	Ramipril & Spironolactone (6)	C4	**18,076**
3	Diclofenac & Perindopril+Indapamide (1)	C0	**15,696**	Omeprazole & Levothyroxine sodium (8)	C3	**15,854**	Omeprazole & Levothyroxine sodium (8)	C3	**17,107**
4	Amiodarone & Metoprolol (4)	C4	**14,547**	Ramipril & Spironolactone (6)	C4	**15,370**	Levothyroxine sodium & Pantoprazole (8)	C3	**16,504**
5	Omeprazole & Levothyroxine sodium (8)	C3	**14,077**	Amiodarone & Metoprolol (4)	C4	**14,909**	Diclofenac & Metoprolol (1)	C0	**15,475**
6	Meloxicam & Metoprolol (1)	C0	**13,781**	Meloxicam & Metoprolol (1)	C0	**13,280**	Naproxen+Esomeprazole & Metoprolol (1)	C0	**14,791**
7	Ramipril & Spironolactone (6)	C4	**13,694**	Naproxen+Esomeprazole & Metoprolol (1)	C0	**12,452**	Amiodarone & Metoprolol (4)	C4	**13,321**
8	Diclofenac & Ramipril (1)	C0	**13,056**	Digoxin & Spironolactone (6)	C3	**12,110**	Meloxicam & Metoprolol (1)	C0	**12,107**
9	Naproxen+Esomeprazole & Metoprolol (1)	C0	**12,005**	Levothyroxine sodium & Pantoprazole (8)	C3	**10,909**	Digoxin & Spironolactone (6)	C3	**11,682**
10	Digoxin & Spironolactone (6)	C3	**11,986**	Diclofenac & Perindopril+Indapamide (1)	C0	**10,424**	Alendronic acid+Colecalciferol & Calcium+Colecalciferol (5)	C3	**9,189**

Table 7. Top 10 interactions in significance level D.

	Drug pair in 2016			**Drug pair in 2017**			**Drug pair in 2019**		
1	Propafenone & Metoprolol (2)	D3	**23,456**	Propafenone & Metoprolol (2)	D3	**24,532**	Metoprolol & Verapamil (2)	D3	**5,048**
2	Metoprolol & Verapamil (2)	D3	**57,27**	Metoprolol & Verapamil (2)	D3	**5,252**	Apixaban & Warfarin (1)	D0	**4,609**
3	Diclofenac & Warfarin (1)	D4	**54,26**	Carbamazepine & Diazepam (3)	D4	**2,850**	Rivaroxaban & Warfarin (1)	D0	**3,906**
4	Carbamazepine & Diazepam (3)	D4	**3,162**	Apixaban & Warfarin (1)	D0	**2,780**	Apixaban & Rivaroxaban (1)	D0	**2,843**
5	Warfarin & Tramadol (1)	D2	**2,751**	Rivaroxaban & Warfarin (1)	D0	**2,565**	Carbamazepine & Diazepam (3)	D4	**2,591**
6	Rivaroxaban & Warfarin (1)	D0	**2,643**	Warfarin & Tramadol (1)	D2	**2,485**	Tramadol & Duloxetine (5)	D0	**2,076**
7	Digoxin & Verapamil (2)	D4	**2,413**	Diclofenac & Warfarin (1)	D4	**2,261**	Carbamazepine & Quetiapine (3)	D4	**2,055**
8	Amlodipine & Carbamazepine (4)	D0	**2,052**	Digoxin & Verapamil (2)	D4	**2,198**	Duloxetine & Codeine+Paracetamol (5)	D0	**2,022**
9	Carbamazepine & Quetiapine (3)	D4	**1,626**	Amlodipine & Carbamazepine (4)	D0	**1,990**	Duloxetine & Nebivolol (4)	D0	**1,618**
10	Tramadol & Duloxetine (5)	D0	**1,591**	Tramadol & Duloxetine (5)	D0	**1,891**	Amlodipine & Carbamazepine (4)	D0	**1,601**

Moreover, the expert marked that the usage of Diclofenac continues to decline, and that may be considered as a positive change.

One of the experts also marked the 2019 combination Alendronic acid+Colecalciferol & Calcium+Colecalciferol because it did not occurred in the 2016 or 2017 top. The concomitant use of these drugs reduces bisphosphonates absorption and could bring about treatment failure. However there is a possibility to avoid DDI. Due to that it is recommended to take drugs with at least two hours break. For instance, bisphosphonates in the morning and drugs, containing calcium and other metal cations in the evening. The right use might be reason why this combination is getting more used.

3.2 Interview results

A total of ten pharmacy professionals (as pharmacist and pharmacy assistant) participated in this study. The interviewees were found by snowball sampling technique and interviews were conducted between March and April 2020. All interviews were audio recorded and carefully transcribed into comparable information form. The original statements of the interviewees were rephrased to shorter phrases, and then were reduced to short and valuable keywords for the better perception of information, which is performed below in Table 8, where is visible, that interviewees were with different sex, occupation, native language, they work in different location, use different software's and have different years of professional experience. However, the interviews did not involve users of MISP because it is a rare software (used only 20 pharmacies in total) and search results did not show MISP users.

The interviewees were selected by willingness to participate and also due to different backgrounds. This was done due to potential different visions and thoughts on the existing system and how pharmacists relate to alert systems and DDIs.

Participants' years of professional experience was between 1.8 years and 14 years. The average length of professional experience was 6.8 years. Interviews lasted between 13 and 25 min per participant, with a mean of 15 min.

Table 8. Background information of interviewees

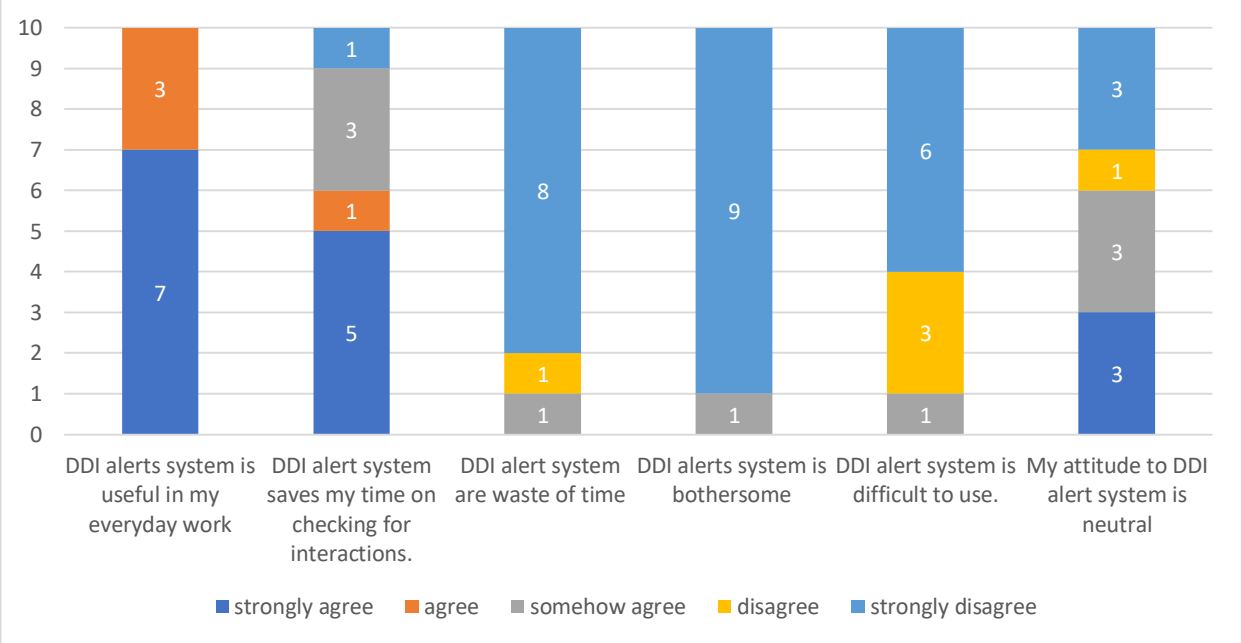
Variable	Case variation	Number of interviewees
Gender	Female	8
	Male	2
Occupation	Pharmacist	8
	Pharmacy assistant	2
Native language	Russian	6
	Estonian	4
Location	Harjumaa	4
	Tartumaa	4
	Ida-Virumaa	2
Pharmacy software	Noom	8
	Hansasoft	2
	MISP	0
Pharmacy chain	Apoteka	5
	Benu Apteek	3
	Euroapteek	2
Years of professional experience	< 5	2
	5-10	8

As it is seen above, most of the interviewees were Noom users. However, 6 participants (60 %) used other systems before: three of participants use in Estonia Noom and Hansasoft, two remembered RAKS as a system, which was used before Noom and Hansasoft and one used software in Norway. Due to that those participants were asked to compare systems. Results showed that all respondents, who used in Estonia different software's preferred more Noom solution because Noom workflow assumes less clicks for the same task. Rask users said that they used it in those times, when there was no DDI alert system. The response of participants, who had a chance to compare solutions in another country replied that Norway systems are too different for comparison, because workflow is more capacious, however, it reduces human error occurrence.

On the question, when participants were asked to specify from which moment they started to use the alert system consciously 10 (100 %) answered that they started to use it consciously when the system was integrated into their everyday workflow. However, three (30%) of participants claimed that if pharmacists do not know how to view information it can be easily skipped and one said that most of his or her colleagues did not know how to use the system properly for some time.

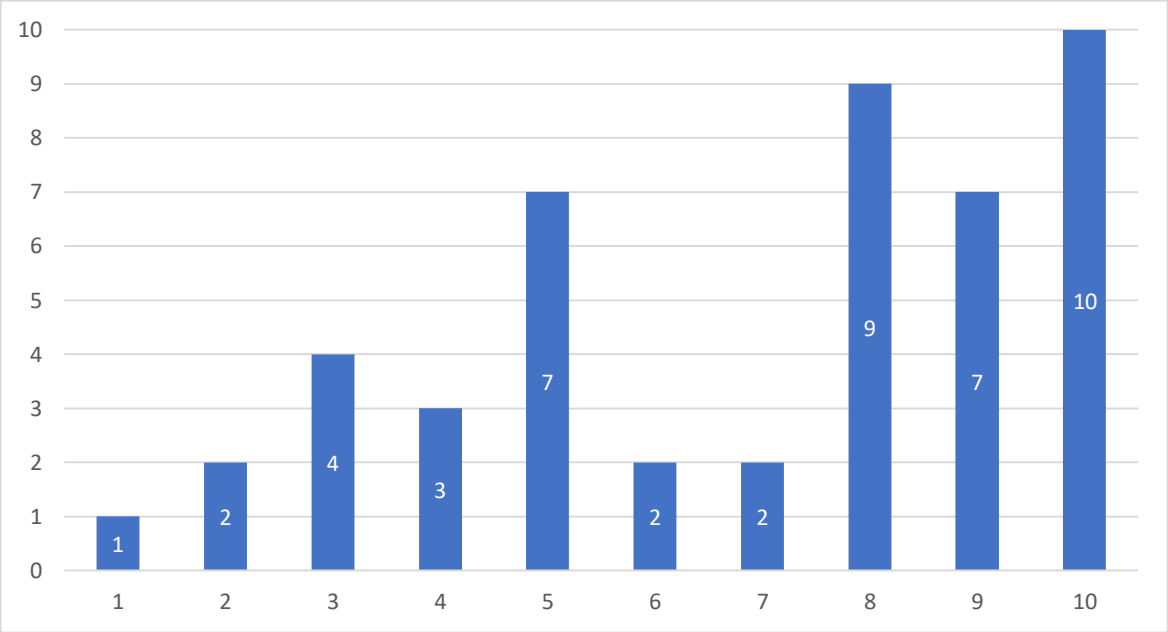
Further, the participants were asked to evaluate statements of DDI alerts on a scale of 5, where 5 is strongly disagree, to 1, strongly agree. The questions and answers are performed in figure 8. Answers show, that pharmacists are mainly positive with the DDI alert system.

Figure 8. Questions and answers or respondents



The interviewees were asked how many DDIs they see in a day. And results are not the same and can be found in figure 9. The results were between 1 DDIs and up to 10 interactions per day. The average was 4.7 DDIs per one working day.

Figure 9. Number of DDIs which happens per one working day.

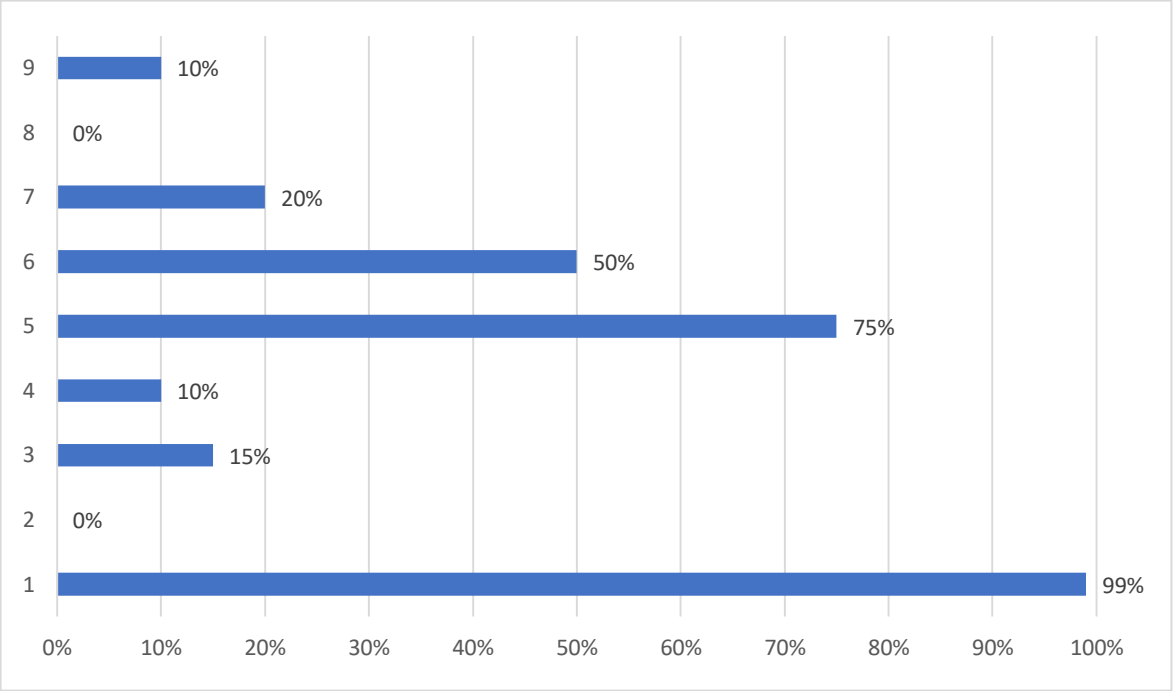


The next question was about elderly patients, and their DDIs. The 5 (50 %) participants replied that the 65+ years old patients DDIs are the same. However, another half of respondents confirm that the older patients, the bigger is chance of DDIs.

To the respondents were also shown a list of top 10 interactions and all participants replied that they do know about those combinations, however, 70% of respondents said that almost half of interactions never happened in their professional work life.

The participants were asked about what is their reaction when software shows DDI. The results showed that 27.9% are skipped (the average) due to interactions known by the user. The results can be seen on figure 10.

Figure 10. How many DDI are skipped by users.



Moreover, the pharmacists were asked about their actions when DDI occurred. 20% of respondents said that they will not say about DDI because they are afraid to scare the patient or due to lack of privacy (due to a queue). 30% of respondents said they will ask a person about this drug-drug combination: where these drugs have been used before or not. If interaction is new, then patients would be asked to observe their health more carefully. In cases when patients used these combination before and no side effects were noticed, then drugs are sold without any comments. However, if a patient names a side effect, which might have occurred due to usage of these drugs, then pharmacist or pharmacy assistant ask to refer to a specialist, who might change medical plan (prescribed medicine). Also the system might show DDI when a person is buying a third person (as family member) non-prescribed medicine, or if a person is buying drugs in a store and is aware which combination should be avoided. 30% of respondents said that they will inform patients about possible DDI and 20% of respondents said that they will inform patients if the patient will ask about possible side effects.

Furthermore, the respondents answered about calls to prescribers (family physicians for example). 30% said that in the beginning of their career they tried to call to doctors if serious

DDI occurred. However, most of the calls were unanswered or medical plan was not changed after this call. 40% said that they could not do anything if drug were prescribed. Others said that they never tried to call prescribers in case of ADRs because they do not have right not to cell or to change situation in this case.

If it was possible to provide alternative drugs for avoidance of DDI, 90 % of respondents would do that. However, not all patients would agree with pharmacists' advice. In this situation pharmacists and pharmacy assistant would not push and sell chosen drugs.

The Noom and Hansasoft users were asked about their use of other methods to check the information about DDI. Information from the State Agency of Medicine (https://ravimiamet.ee/en) – is a choice of 20% of respondents, INXBASE- 20%, Medscape (https://www.medscape.com) - 20%, Drugs.com (https://www.drugs.com/) - 20%, SafeFetus (https://www.safefetus.com/), and Google (www.google.com) - 20%. Some answers consisted of a few solutions.

The 90% of participants would not support DDI alert system removal but offers to change were:

- Complement information about DDI, so users will lose meaning to check information on other sources (as Medscape, Drugs.com, etc.)
- Bigger font and bold text for key information
- Less clicks – the more efficient use of time. The key information is preferable to be on the main screen.

3. Discussion

The number of significant DDIs, as level C and D is 31,4 % (33,1 % in 2016, 31,5% in 2017 and 29,7% in 2019). That means that DDI stays on approximately the same level but there is a positive decreasing trend with the most significant levels (C4 and D4). The absence of 2018 in this context does not interfere, as a comparison of the 2016 vs 2019 is possible. However, the lack of 2018 data is distracting the second hypothesis-the influence of pharmacists on DDI occurrence.

In a previous study, which can be compared with current work, is Metsla's research that evaluated family physician prescribing habits and number of clinically significant interacting drugs per one month from June 2016, January 2017, June 2017 and January 2018 showed around 35% of DDI out of all prescriptions. The percent in the previous study is higher, however the results in this section barely can be compared. The results show different percentages because period duration is different and in the studies are used different years and months, as 2018, June and January in Metsla's and 2019 September - November in current study. However, the conclusion can be made that if the duration of the investigated period would be the same then the percentage will be approximately the same in both studies (Metsla, 2018).

The average number of prescriptions, showed that C and D level DDI combinations in analyzed years is around seven per one patient in 2016, 2017 and 2019. The same number can be found in Metsla's study as seven-eight per one patient. That means that drugs per patient stays relatively the same and the different analyses show approximately the same result. However, the amount of interactions per one patient in reality might be different. The study did not focus on more detailed analysis (for example the age and how much drugs per one patient is used). That can be done in the future studies. It can help identify what is the most often occurring number of drugs per one patient, the maximum of drugs per one patient and in which age it mainly happens.

The analysis identified the top 10 most often occurring DDI, level C and D and the results showed that most interactions in analyzed years have many similarities in occurring interactions. However, they are not identical. Moreover, results of 2016 and 2017 have more

similarities than 2019 with previously named years. The Metsla's study showed that the top 10 of clinically significant interactions also stayed relatively the same with a few exceptions.

Due to experts 2019 looks more different because of next changes:

- Group classification changes.
- Some drugs are less likely to be used.

For example the most often C3 level combination in 2019 is Metoprolol & Propafenone. However, the same combination was classified as D3 level in 2016 and 2017. The decision was made not by Estonia specialists and is distributed with other INXBASE users. This kind of decision is done after researches which proves or disproves existing classification.

Moreover, the usage of Diclofenac continues to decline, and that is also positive changes. The EMA and FDA warns that side effects might be serious. For example, Diclofenac can increase risk of heart attack, heart failure, or even bring patient to stroke. Moreover, the risk may be higher if patient have another risk factors for heart disease, such as high blood pressure (*Healthline and EMA*).

Also the less used drug in this top is Warfarin. Expert reply that new anticoagulants could be far safer rather than the commonly-prescribed Warfarin. Due to that can be seen changes in top 10 C level interactions, however D level with Warfarin stays still relatively high in the list. For example interactions as Warfarin interaction with Rivaroxaban or Apixaban. That might happen because doctors do not always cancel old prescriptions, or cannot cancel it because the prescription is done by another doctor. The canceled prescription will be taken into statistics, if the patient bought a prescribed drug and usage of drug is not taken into count. In this case, the alert system will show significant DDI. Due to that, EHIF have plans for the future to allow cancel prescriptions, which was prescribed by another doctor. That will help to reduce the amount of false DDIs.

According to the respondents' answers, the pharmacy professionals (as pharmacist and pharmacy assistant) mostly find an alert system as a positive attachment to their everyday work. However, most participants replied that they were aware of the most often occurring DDIs before the alert system was implemented but alert systems might control and remind if

some combination of drugs are forgotten or it is a new drug, which side effects are not yet well known by heart by pharmacists. Furthermore, the pharmacist need to decide by themselves how solve case, when significant DDI occurred. Pharmacists probably will carefully warn patient. However, in the majority will not dispute if DDI happened between prescribed drugs because they cannot reject the sale if the drug is prescribed. Due to that it is difficult to influence on significant DDI from the pharmacists side.

Furthermore, the pharmacists often replied in the interviews that they feel that the patient is mainly a client and wants to get service. And if the pharmacist or pharmacy assistant will dispute the prescriber's decision then the patient will choose another pharmacy for future purchase.

However, some of pharmacists tried to call to prescribers for first time when they noticed significant DDI and was not sure it. They replied that:

- Drug combination was never changed
- It was quite difficult to reach the prescriber due a busy timetable or time when the patient visits the pharmacy (after the end of the prescribers working day).

However, the pharmacist and pharmacy assistants are still very important links in the system and they can and reduce potential harm. For example, there is a big possibility that the patient would be more likely asked about previously used drugs. If a patient already used a drug combination, which might cause DDI and did not notice any negative changes in state of health while drugs were used then the drug will be purchased to the patient without further recommendations. If a patient did not use drugs which might trigger DDI then the pharmacist or pharmacy assistant with the likelihood asks to pay attention to their state of health and if the patient will notice harmful changes then better contact their family physician and describe symptoms. That can help to change treatment plans and not frighten patients without need.

Due to that system is taken as a positive attachment to the everyday working process, however it should be developed. For example, pharmacists were interested in the more complement information about DDI, so users will lose meaning to check information on other sources, bigger front and bold text for key information and less clicks – the more efficient

use of time. The pharmacist also replies that sometimes systems have delays and they have many patients in the queue they will not click and open DDI reminders. In this case the most important information is better to be done with a minimal amount of clicks.

The respondent group was varied enough, however, there is advice that can be done for the future studies. It is advisable to add MISP users, interview more Hansasoft users and add pharmacists, who are in pre-retirement age. Moreover, the respondents claimed that Noom has less clicks for the same action. Due to that there might be technical comparison of the different systems used in Estonia. That might help detect systems weak and strengths and identify the possible improvements.

Finally, it is good to note that a DDI alert system is established for the potential harm minimization. System has a positive impact on the patients' safety and on pharmacy specialists' everyday work. However, alert systems need to be further developed for the best possible solution.

5. Summary

The aim of the thesis was to analyze top 10 drug-drug interactions (DDIs) level C and D, which occurred in 2016-2019 in the three months interval. Furthermore, the thesis focuses on alert system development via Estonian pharmacy professionals by their impact on interactions via computerized alert systems: as their attitude towards and suggestions for improvement of existing systems.

Two researches were conducted. For quantitative research data from EHIF were analyzed and top 10 D and C Drug-Drug interactions which occurred during a three month period in September - November 2016, 2017 and 2019 were identified. Results show that the number of significant drug-drug interactions as level C and D stayed on the same level through the entire investigated period. Moreover, the interactions have many similarities, however they are not identical and do not stay in the same position in top 10 interactions.

The qualitative research was performed by interviews with pharmacists and pharmacy assistants. Some interviews were done face-to-face but some of them were conducted by real-time videoconferencing due to COVID-19. The pharmacy specialists were with different backgrounds, as work experience, used system, location, etc. Results showed that pharmacists do not significantly influence the interactions between prescribed drugs. Because pharmacists do not dispute if drugs which show interaction are prescribed. Due to that, pharmacists do not influence significantly on C and D level interactions. However, an alert system has positive impact and can be used if interaction happened between prescribed and non-prescribed medication. In this case pharmacists have more chances to prevent potential harm to patients.

The study provides valuable information to the drug-drug information systems usage among pharmacists. The study results will be shared with Estonian Health Insurance Fund and all who will express interest to study can familiarize with results.

References

Astro Baltics (2020). E-Health.
[WWW] https://www.astrobaltics.eu/en/e-tervishoid-2/(19.04.2020)

Baysari, M.,T., Zheng,W., Y., Li, L., Westbrook, J., Day, R., O., Hilmer, S., Dort, B., A., V., Hargreaves, A., Kennedy, P., Monaghan, C., Doherty, P., Draheim,M., Nair, L., Samson, R. (2019).Optimising computerised decision support to transform medication safety and reduce prescriber burden: study protocol for a mixed-methods evaluation of drug–drug interaction alerts - *BMJ Open.*
[WWW] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6701635/#R3 (19.04.2020)

Brody, T. (2017). FDA's Drug Review Process and the Package Label. Strategies for Writing Successful FDA Submissions – *ScienceDirect*
[WWW] https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/drug-drug-interaction. (19.04.2020)

Bucşa, C., Farcaş, A., Cazacu, I., Leucuta, D., Achimas-Cadariu, A., Mogosan, C., Bojita, M. (2012). How many potential drug-drug interactions cause adverse drug reactions in hospitalized patients? - *European Journal of Internal Medicine.* [WWW] https://www.ejinme.com/article/S0953-6205(12)00249-X/pdf (19.04.2020)

Böttiger, Y., Laine, K., Andersson, M., L., Korhonen, T., Molin, B., Ovesjö, M., Tirkkonen, T., Rane, A., Gustafsson, L., L., Eiermann, B. (2008).SFINX – A drug-drug interaction database designed for clinical decision support systems-*European Journal of Clinical Pharmacology*
[WWW] https://www.researchgate.net/publication/23996386_SFINX_-_A_drug-drug_interaction_database_designed_for_clinical_decision_support_systems (19.04.2020)

Cascorbi, I. (2012). Drug Interactions—Principles, Examples and Clinical Consequences - *Deutsches Ärzteblatt International.*
[WWW] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3444856/ (19.04.2020)

Das, S.,Behera, S., K., XavierA., S., Dharanipragada, S., Selvarajan S. (2019). Are drug-drug interactions a real clinical concern? – *PubMed.*
[WWW] http://www.picronline.org/article.asp?issn=2229-3485;year=2019;volume=10;issue=2;spage=62;epage=66;aulast=Das#ref (19.04.2020)

Duodecim Terveysportti (2017). Terveysportin SFINX-PHARAO on nyt Lääkeinteraktiot ja –haitat.
[WWW]https://www.terveyskirjasto.fi/terveysportti/uutismaailma.duodecimapi.uutisarkisto?p_arkisto=1&p_artikkeli=uux21492 (19.04.2020)

Eesti Haigekassa (2018). Ravimite koostoimete andmebaasi juurutamine pälvis rahvusvahelise tunnustuse
[WWW]https://www.haigekassa.ee/uudised/ravimite-koostoimete-andmebaasi-juurutamine-palvis-rahvusvahelise-tunnustuse (19.04.2020)

Eurostat (2020). Self-reported use of prescribed medicines by sex, age and educational attainment level.
[WWW]https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_ehis_md1e&lang=en (19.04.2020)

EMA (2013). Diklofenak – uued vastunäidustused ja hoiatused pärast Euroopa Ravimiameti kardiovaskulaarse ohutuse hinnangut
[WWW]Diklofenak - ohutusalane teave.pdf (19.05.2020)

Hansasofti apteegi infosüsteemi integreeritud ravimite koostoime andmebaasi kasutusjuhend.
[WWW] New folder\Kasutusjuhend Koostoimed SFINX.pdf (16.05.2020)

Healthline (2020). Diclofenac, Topical Gel
[WWW]https://www.healthline.com/health/diclofenac-topical-gel#alternatives (19.05.2020)

Indermitte, J., Beutler, M., Bruppacher, R., Meier C., R., Hersberger, K., E. (2007). Management of drug-interaction alerts in community pharmacies - *Journal of Clinical Pharmacy and Theraperutics.*
[WWW]https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2710.2007.00802.x (19.04.2020)

Koostoimete kontroll tarkvaras „Noom 2.0“
[WWW] Koostoimete_kontroll_2_0.pdf (16.05.2020)

Köhler, G., Bode-Böger, S., Busse, R., Hoopmann, M., Welte, T., Böger (2000). Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use- *PubMed*.
[WWW] https://www.ncbi.nlm.nih.gov/pubmed/11097142 (19.04.2020)

Kwak, A., Lee, E., Oh, J., M., Ji, E., Kim, K. (2019). Perspectives of Non-Pharmacy Professionals in Long-Term Care Facilities on Pharmacist-Involved Medication Management in South Korea: A Qualitative Study
[WWW]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6603902/#__ffn_sectitle (19.04.2020)

Létinier,L., Cossin, S., Mansiaux,Y., Arnaud,M., Salvo, F.,Bezin, J., Thiessard, F., Pariente, A. (2019). Risk of Drug-Drug Interactions in Out-Hospital Drug Dispensings in France: Results from the DRUG-Drug Interaction Prevalence Study- *frontiers in Pharmacology*
[WWW] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6438853/#!po=1.85185 (19.04.2020)

Medbase (2017). Material for distributors. INXBASE and RISKBASE.

[WWW] https://www.medbase.fi/en/material-distributors/sfinx-pharao/ (19.04.2020)

Metsla, K. (2018). Estonian family physicians usage and satisfaction with drug-drug interaction alert system.
[WWW] https://digikogu.taltech.ee/et/Item/b7f719e9-d530-4f6c-9283-ae6092993cf8 (13.05.2020)

Multirec (2020). MR-interactions. Significant drug interactions.
[WWW] https://www.multirec.fi/products/mr-interactions/ (19.04.2020)
Olsen, R., M., Sletvold, H. (2018). Potential drug-to-drug interactions: a cross-sectional study among older patients discharged from hospital to home care - *Safety in Health* [WWW] https://safetyinhealth.biomedcentral.com/articles/10.1186/s40886-018-0075-z (19.04.2020)

Palleria, C., Paolo, A., Giofrè, C., Caglioti, C., Leuzzi, G.,Siniscalchi, A., Sarro, G., Gallelli, L. (2013). Pharmacokinetic drug-drug interaction and their implication in clinical management. - *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences*.
[WWW] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3897029/#__ffn_sectitle (19.04.2020)

Phellas,N., Bloch, A., Seale, C. (2011).structured methods: interviews, questionnaires and observation.
[WWW]https://www.sagepub.com/sites/default/files/upmbinaries/47370_Seale_Chapter_11.pdf (02.05.2020)

Roblek, T., Vaupotic, T., Mrhar, A., Lainscak, M. (2015). Drug-drug interaction software in clinical practice: a systematic review- *European Journal Clinical Pharmacology*.
[WWW] https://www.ncbi.nlm.nih.gov/pubmed/25529225 (19.04.2020)

Sijs, H., Aarts, J., Vulto, A., Berg, M. (2006). Overriding of Drug Safety Alerts in Computerized Physician Order Entry-*Journal of the American Medical Informatics Association*.
[WWW] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1447540/ (19.04.2020)

Strandell, J., Bate, A., Lindquist M., Edwards, R. (2007). Drug–drug interactions – a preventable patient safety issue? - *British Journal of Clinical Pharmacology*.
[WWW] https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2125.2007.02981.x (19.04.2020)

Terviseameti registrid (2020). Statistika
[WWW] http://mveeb.sm.ee/ctrl/ee/Statistika/show/3?statistika=1&otsi=N%C3%A4ita (19.04.2020)

Tilson, H., Hines, L., E., McEvoy, G., Weinstein, D., M., Hansten, P., D., Matuszewski, K., le Comte,M., Higby-Baker, S., Hanlon, J., T.,Pezzullo, L., Vieson, K., Helwig, A., L., Huang, S., Perre, A., Bates, D., W., Poikonen, J., WittieM., A.,, , Grizzle, A., J., Brown, M., Malone D., C. (2016)Recommendations for Selecting Drug-Drug Interactions for Clinical Decision Support. *American Journal of Health-System Pharmacy*.
[WWW] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5064943/ (19.04.2020)

Appendix 1- Interview guide in English

Introduction

I want to thank you for taking the time to meet with me today. My name is Aljona Kurbatova. I'm a student of Tallinn Technical University (TalTech) and my master program is called Health Care Technology. I would like to talk to you about your experience in use of Drug-Drug interactions (DDIs). The purpose of this in-depth interview is to hear your thoughts and opinions about DDIs alert system from pharmacist-involved perspective. The interview will take less than an hour. This interview will be audio recorded because I do not want to miss any of your comments. Although I will be taking some notes during the session, I can't write fast enough to get it all down. We are on tape, so please be sure to speak up so that we don't miss your comments. All responses will be kept confidential. This means that your interview responses will only be shared with research team members and we will ensure that any information we include in our report does not identify you as the respondent. There are no right or wrong answers to my questions. Please feel free to share your opinions. Remember, you don't have to talk if you do not want to and you may end the interview at any time. Are there any questions about what I have just explained? Are you willing to participate in this interview?

Questions

1. How many years is your practicing experience? (Age, occupation, location, mother tongue?) Please specify your profession? Are you pharmacist or pharmacy assistant?
2. Do you work somewhere else besides pharmacy? Have you ever worked outside of Estonia? Did you participate in Erasmus (internship)? If so, did you see alert systems there?
3. Which one (NOOM, Hansasoft or MISP)? Did you use other systems? Can you please specify from which moment you started to use the alert system consciously?
4. What do you think about the current alert system? Can you please evaluate the next statement of DDI alerts on a scale of 5, where 5 is strongly disagree, to 1, strongly agree?

- DDI alerts system is useful in my everyday work
- DDI alert system saves my time on checking for interactions.
- DDI alert system are waste of time
- DDI alerts system is bothersome
- DDI alert system is difficult to use.
- My attitude to DDI alert system is neutral.

5. Roughly how many DDI alerts do you see in a day? (In a month?)

- Can you please specify how old are people who have DDIs in the alert system?
- How often in your everyday work you see next interactions:

1. Diclofenac & Metoprolol
2. Torasemide & Warfarin
3. Meloxicam & Metoprolol
4. Diclofenac & Perindopril + Indapamide
5. Metoprolol & Amiodarone
6. Spironolactone & Ramipril
7. Omeprazole & Levothyroxine sodium
8. Naproxen + Esomeprazole & Metoprolol
9. Spironolactone & Digoxin
10. Diclofenac & Ramipril Metoprolol & Propafenone
11. Metoprolol & Propafenone
12. Metoprolol & Verapamil
13. Diclofenac & Warfarin
14. Tramadol & Warfarin
15. Diazepam & Carbamazepine
16. Verapamil & Digoxin
17. Rivaroxaban & Warfarin
18. Apixaban & Warfarin
19. Carbamazepine & Amlodipine
20. Tramadol & Duloxetine

- Can you please name the most DDI (without prescription)?

6. Do you read the alerts?
7. Do you skip any alerts? Which ones and why? How big is percent of those, which you read thoroughly? How big is the percentage of alerts, which you ignore approximately?
8. Can you please name the most often happened DDI and explain why they were memorable?
    - What are the most common interactions among older people and is there any difference with other interactions in general, or are there any other interesting aspects that a pharmacist can say about elderly patients (65+ years)?
9. Do you tell patients what DDIs occurred in his/her case? (Even if reaction is minor)?
10. Do you provide alternative drugs for patients to avoid DDIs?
11. Do you use other methods to check the level of DDIs? If so, which ones?
12. If there was an option to remove DDI alerts from the EMMS, would you support their removal? Why?

How might the alert system be improved? Please name 3 main changes

Closing

Is there anything more you would like to add? Thank you for your time.

Appendix 2 - Interview guide in Russian

Вступительная часть

Здравствуйте, я хочу начать интервью со слов благодарности за то, что вы согласились уделить мне время. Моё имя – Алёна Курбатова. Я студентка Таллинского Технического Университета, моя специальность называется Технология здравоохранения. Интервью проводится в связи использованием вами системы оповещения в случае возникновения лекарственного взаимодействия. Цель этого интервью – это услышать ваше мнение и соображения по поводу существующей системы с точки зрения фармацевта/провизора. Интервью займет примерно час вашего времени. Во время нашего разговора я буду делать пометки, но боюсь, я не настолько быстро пишу, чтобы записать всю интересующую меня информацию. По этой причине интервью будет записано, потому что я не хочу пропустить ничего из того, что было вами сказано. Наш разговор записывается, поэтому, пожалуйста, говорите достаточно громко, чтобы ваши ответы были слышны на записи. Все, что мы с вами будем обсуждать будет конфиденциально. Это означает, что ваши ответы на интервью будут переданы только членам исследовательской группы, и мы гарантируем, что любая информация, включенная в наш отчет, не будет идентифицировать вас как опрошенного. На вопросы нет правильных или неправильных ответов. Пожалуйста, не стесняйтесь высказывать своё мнение. Помните, что вы не должны говорить, если вы не хотите этого, и вы можете закончить интервью в любой момент. Есть ли у вас какие-либо вопросы по поводу того, что я только что сказала? Готовы ли вы принять участие в этом интервью?

Вопросы

1. Какой у вас профессиональный стаж? (ваш возраст, в каком городе вы работаете, ваш родной язык). Пожалуйста утоните свою профессию. Вы провизор или фармацевт?
2. Работаете ли вы еще где-то помимо аптеки? Работали ли вы когда – то за пределами Эстонии? Возможно, вы выезжали на практику за границу при помощи программы Erasmus? Если да, то использовалась ли похожей системой оповещения о лекарственном взаимодействии?

3. Какой системой вы пользуетесь (NOOM, Hansasoft или MISP)? Использовали ли вы другие системами? Можете пожалуйста уточнить, когда вы начали осознанно пользоваться всплывающим напоминаниями осознанно в случае возникновения лекарственного взаимодействия?
4. Можете, пожалуйста, оценить систему оповещения взаимодействий на сегодняшний день? Можете, пожалуйста, оценить утверждения по 5 шкале, где 5 означает, что вы категорично не согласны с утверждением и 1 – вы абсолютно согласны с высказыванием?
    - Система оповещения лекарственного взаимодействия помогает в моей ежедневной работе
    - Система оповещения экономит рабочее время на проверку взаимодействий.
    - Система оповещения лекарственного взаимодействия тратит мое время в пустую
    - Система оповещения лекарственного взаимодействия надоедливая
    - Систему оповещения лекарственного взаимодействия сложно использовать
    - Мое отношение к системе оповещения нейтральное
5. Примерно сколько раз за день вы видите информацию о лекарственном взаимодействии? (В месяц?)
    - Можете, пожалуйста, уточнить, какой возраст у людей, у которых чаще всего возникает предупреждение о взаимодействии?
    - Часто ли в вашей практики вы видели следующие взаможействия:

1. Diclofenac & Metoprolol
2. Torasemide & Warfarin
3. Meloxicam & Metoprolol
4. Diclofenac & Perindopril + Indapamide
5. Metoprolol & Amiodarone
6. Spironolactone & Ramipril
7. Omeprazole & Levothyroxine sodium
8. Naproxen + Esomeprazole & Metoprolol

9. Spironolactone & Digoxin
10. Diclofenac & Ramipril Metoprolol & Propafenone
11. Metoprolol & Propafenone
12. Metoprolol & Verapamil
13. Diclofenac & Warfarin
14. Tramadol & Warfarin
15. Diazepam & Carbamazepine
16. Verapamil & Digoxin
17. Rivaroxaban & Warfarin
18. Apixaban & Warfarin
19. Carbamazepine & Amlodipine
20. Tramadol & Duloxetine

- Какие самые частые взаимодействия вы можете назвать (без рецепта)?

6. Вы читаете предупреждения?
7. Пропускаете ли вы какие-либо предупреждения о возникшем взаимодействии? Если да, то какие и почему? Насколько большой процент предупреждений, которые вы читаете тщательно? Приблизительно какой процент предупреждений вы игнорируете?
8. Можете ли вы назвать наиболее частые взаимодействия и назвать причину, почему именно эти взаимодействия вам запомнились?

    - Какие у пожилых людей интеракции встречаются чаще всего и вообще чем отличаются у них интеракции или есть еще какие-то интересные аспекты, которые аптекарь может вынести у пожилых людей (65+ лет)?

9. Говорите ли вы пациенту, что в его случае возникло предупреждение о взаимодействии медикаментов? Даже если уровень возможной реакции минимален? В других случаях?
10. Предлагаете ли вы пациенту альтернативный медикамент во избежание взаимодействия лекарств?
11. Используете ли вы другие способы, которые помогают вам проверять уровень опасности взаимодействия? Если ответ да, то какие?

12. Если бы была возможность убрать оповещения, поддержали ли бы вы отказ от данной системы? Почему?
13. Опишите пожалуйста, как конкретно на компьютере выглядит система оповещения, удобно/неудобно ли ей пользоваться, где она располагается на экране и другие детали.
14. Как система может быть улучшена? Назовите 3 главных изменения.

Окончание беседы

Есть ли что-то, что вы хотите добавить и прокомментировать? Большое спасибо, что уделили мне время.

Appendix 3- Interview guide in Estonian

Vestluse juhend

Sissejuhatus

Tänan, et leidsite aega kohtuda. Minu nimi on Aljona Kurbatova. Olen Tallinna Tehnikaülikooli magistrant, kes õpib Tervisetehnoloogiate erialal. Tahaksin teiega rääkida ravimite koostoimete hoiatussüsteemist. Intervjuu eesmärgiks on küsida teie arvamust professionaalsest ehk farmatseudi/proviisori vaatenurgast ravimite koostoime hoiatussüsteemi kohta. Intervjuu võtab aega kuni 60 minutit. Intervjuu käigus teen küll kirjalikke märkmeid, kuid kuna ma ei jõua üles kirjutada kõike, millest räägime paluksin ka luba meie vestlust salvestada. Seepärast paluksin teil ka rääkida võimalikult kõva ja selge häälega, et hiljem oleks vastused ja kommentaarid hästi kuuldavad. Kõik teie vastuseid hoitakse konfidentsiaalsena ja kasutatakse anonüümselt. See tähendab, et teie vastuseid jagatakse ainult uurimisrühma liikmetega ja tagame, et intervjuu käigus kogutud andmeid ja vastuseid ei seostata uurimistöö koostamisel ühegi konkreetse isikuga. Rõhutan, et minu küsimustele ei ole õigeid ega valesid vastuseid, seega palun vabalt oma arvamust jagadat. Pidage meeles, et kui te mõnele küsimusele vastata ei soovi, siis seda ka tegema ei pea ja teil on õigus lõpetada intervjuu igal ajal, kui te soovite. Kas teil on küsimusi uuringu või intervjuu kohta? Kas te olete nõus intervjuus osalema?

Küsimused

1. Mitu aastat on teil töökogemust? (Vanus, asukoht, emakeel?) Palun täpsustage oma ametit. Kas te olete farmatseut või proviisor?

2. Kas töötate lisaks kuskil mujal? Kas olete kunagi töötanud väljaspool Eestit? Kas osalesite Eramuse praktikas? Kui jah, kas kasutasite seal sarnast hoiatussüsteemi?

3. Missugust süsteemi te kasutate (kas NOOM, Hansasoft või MISP)? Kas kasutasite muid süsteeme? Kas oskate täpsustada, millal te hakkasite hoiatussüsteemi teadlikult kasutama?

4. Mida arvate hoiatussüsteemist, mida te kasutate? Palun hinnata järgmised väited, kus 5 on „mitte nõus“ ja 1 tähendab „nõustun täielikult“.

- Koostoimete kuvamise süsteem on minu igapäevases töös kasulik
- Koostoimete kuvamise süsteem säästab mu aega ravimite koostoimete kontrollimisel
- Koostoimete kuvamise süsteem on aja raiskamine
- Koostoimete kuvamise süsteem on koormav
- Ravimite koostoimete kontrollimise süsteemi on keeruline kasutada.
- Ma suhtun ravimite koostoimete kontrollimise süsteemi neutraalselt.

5. Kui palju ravimite koostoimeid te näete päevas/ kuus?

    - Kas te oskate täpsustada, kui vanad on inimesed, kellel esinevad hoiatused ravimite koostoime süsteemis kõige sagedamini?
    - Kui tihti Teie töös Te nägite järgmised koostoimed:

1. Diclofenac & Metoprolol
2. Torasemide & Warfarin
3. Meloxicam & Metoprolol
4. Diclofenac & Perindopril + Indapamide
5. Metoprolol & Amiodarone
6. Spironolactone & Ramipril
7. Omeprazole & Levothyroxine sodium
8. Naproxen + Esomeprazole & Metoprolol
9. Spironolactone & Digoxin
10. Diclofenac & Ramipril Metoprolol & Propafenone
11. Metoprolol & Propafenone
12. Metoprolol & Verapamil
13. Diclofenac & Warfarin
14. Tramadol & Warfarin
15. Diazepam & Carbamazepine

16. Verapamil & Digoxin
17. Rivaroxaban & Warfarin
18. Apixaban & Warfarin
19. Carbamazepine & Amlodipine
20. Tramadol & Duloxetine

6. Kas te loete teateid?

7. Kas mõned teated te jätate vahele? Millised ja miks? Kui suur on protsent neist, mida te põhjalikult loete? Kui suur on teavete protsent, mida te jätate tähelepanuta?

8. Palun nimetage koostoimeid, mis teil on meelde jäänud, et ilmuvad teile kõige sagedamini ja miks nad jäid teile meelde?

    - Millised on vanemate inimeste seas kõige levinumad koostoimed ja kas on mingi erinevus teiste vanusegruppides või kas on muid huvitavaid aspekte, mida Te oskate öelda (+ 65 a.)?

9. Kas te ütlete patsiendile, kui süsteem näitab, et võib tekkida ravimite koostoime? (Isegi kui reaktsioon on väike)? Aga teistes olukordades?

10. Kui süsteem näitab ravimite vahel koostoimet, kas te pakute kliendile alternatiivset ravi selleks, et vältida negatiivseid tagajärgi?

11. Kas te kasutate teisi süsteeme selleks, et vältida ravimite koostoimed? Kui jah, siis missugused need on?

12. Kui teil oleks võimalus lülitada ravimite koostoime hoiatussüsteemi välja, kas te toetaksite seda?

13. Kuidas ravimite koostoime süsteem võiks teie arvates olla kaasajastatud? Palun nimetage 3 aspekti.

Lõpetamine

Kas soovite veel midagi lisada? Täname teid teie aja eest.