Outi Laatikainen

MEDICATION-RELATED ADVERSE EVENTS IN HEALTH CARE
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Abstract

Medication-related adverse events include adverse drug events either directly or indirectly related to the drug’s pharmacology, as well as medication errors, i.e. errors in the medication process. Medication-related adverse events are common issue in both the inpatient and outpatient setting affecting approximately 20% of hospitalized patients and causing 3-5% of unplanned hospital admissions in the adult population. Although medication-related adverse events are common in all age groups, geriatric patients have been found especially susceptible to them. With the estimates of increased life expectancy and higher consumption of medicines in the future, there has been a growing pressure for more efficient detection and prevention of medication-related adverse events.

The objective of this study was to form a comprehensive overview of medication-related adverse events around the Finnish tertiary care by describing both adverse drug events and medication errors occurring in this setting. The results of this research project demonstrated that adverse drug events affect approximately every fifth patient during hospital admission and that one third of these events are preventable. Most of adverse drug events and medication errors occur with medicines from commonly used ATC groups, the largest group being the N (Nervous class) medicines. Medication-related adverse events were also identified as a burdening factor to the health care organizations, as it was estimated that 23% of the unplanned geriatric hospital admissions resulted from adverse drug events.

This research project was the first to describe the overall situation of medication-related adverse events in the Finnish tertiary care by utilizing the national medication safety incident report (Haipro) data. It emphasized the importance of medication safety research in the development of adverse event detection and prevention methods. The results of this research project create opportunities for further development of both national medication safety and patient safety.

Keywords: adverse drug event, health care, medication error, medication safety, patient safety, pharmacoepidemiology, tertiary care
Laatikainen, Outi, Lääkkeisiin liittyvät haittatapahtumat terveydenhuollossa.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research
Center Oulu; Oulun yliopistollinen sairaala
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Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä
Lääkkeisiin liittyviin haittatapahtumiin luetaan sekä lääkkeen farmakologiaan suorasti tai epä-
suorasti liittyvät lääkehaitat, että lääkehoidon prosessin virheinä ilmenevät lääkityspoikkeamat. Lääkehaitat ja lääkityspoikkeamat ovat yleinen ongelma sairaaloissa ja 20 % sairaalassa hoidetut potilaat ja aiheuttavat arviolta 3-5 % kaikista aikuiskäytössä olevista lääkityspoikkeamista. Vaikka lääkehaittoja esintyy yleisesti koko väestön tasolla, ovat ikääntymisen vaikutteella lääkkeiden kasvavalla kululla lääke- ja potilaat aikuisia ja vanhia erityisen alttina. Väestön ikääntymisen muutos sekä lääkkeiden kasvava kulutus ovat sekä lääkkeisiin liittyvistä haittatapahtumista että tehostettavissa tulevissa lääkityspoikkeamissa.

Tämän työn tarkoituksena oli muodostaa kokonaiskäsitys lääkkeisiin liittyvistä haittatapahtumista ja lääkehaittojen ja lääkityspoikkeamien ilmenevistä sairaalanhoidossa. Työssä lääkehaittoja havaittiin arviolta joka viides erikoissairaanhoitoalueella. Kolmasosa lääkehaittoista arvioitiin ennalla, ja lääkityspoikkeamien osalta oli lääkkeistä enemmän laajempi kannatus. Suurin osa lääkityspoikkeamista oli ollut N-ryhmän lääkkeet. Lääkehaittojen havaittujen otosten arvion mukaan lääkehaittojen ja lääkityspoikkeamien ilmeneville lääkkeisiin liittyvien haittatapahtumien ongelmassa on ollut lääkkeiden kasvava kulutus, joka aiheuttaa lääkkeisiin liittyviä haitatapahtumia.
“Primum Non Nocere” - Hippocrates
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I would also like to thank my pre-examiners, professor emeritus Risto Roine and professor Katri Vehviläinen-Julkunen, for providing comments and corrections for this thesis. They have been greatly valued. Professors Jukka Hakola, Helvi Kyngäs, and Markku Savolainen are also greatly acknowledged for their guidance in my follow-up group. I also want to thank professor Jukka Hakola, the head of the department, for providing a working place with warm and inspiring atmosphere. I want to express my gratitude to Julia Swan for the language revision of my thesis and to Sanjay Patel for the language revision of my publications.

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Most of all, I wish to thank my family. Dad, thank you for being the one person in this world never questioning the value of education. Vaari, thank you for saying it like it is: not ever has studying anything been useless and not once has anything in this world been ruined with sugar. Sami and Miko, I thank you for your tolerance and understanding during these years. Sami, your unwavering support, incredible patience and endless love through the good, the bad, and most of all, the crazy times has often been the only thing that kept me going. I owe everything to you. Miko, thank you for showing up and changing my life forever. You simply didn’t allow me to get lost in this work and showed me what is truly important in this life. I love you dearly.

Oulu, 20.1.2020

Outi Laatikainen
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADE</td>
<td>Adverse Drug Event</td>
</tr>
<tr>
<td>Adm</td>
<td>Admission</td>
</tr>
<tr>
<td>ADME</td>
<td>Absorption, Distribution, Metabolism, Excretion; the variables forming the basic functions in drug pharmacokinetics</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomic Therapeutic Classification</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>DDI</td>
<td>Drug-Drug Interaction</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency Department</td>
</tr>
<tr>
<td>EHR</td>
<td>Electronic Health Record</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>FADR</td>
<td>Fatal Adverse Drug Reaction</td>
</tr>
<tr>
<td>Fimea</td>
<td>The Finnish Medicines Agency</td>
</tr>
<tr>
<td>FSPS</td>
<td>the Finnish Society for Patient Safety</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GTT</td>
<td>Global Trigger Tool</td>
</tr>
<tr>
<td>Haipro</td>
<td>Medication Safety Incident Reporting System</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases, 10&lt;sup&gt;th&lt;/sup&gt; Revision</td>
</tr>
<tr>
<td>ICH</td>
<td>the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
</tr>
<tr>
<td>IT</td>
<td>Information Technology</td>
</tr>
<tr>
<td>LASA</td>
<td>Look Alike, Sound Alike, referring to a group of high-risk medicines</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of Stay in hospital</td>
</tr>
<tr>
<td>MD</td>
<td>Median</td>
</tr>
<tr>
<td>ME</td>
<td>Medication Error</td>
</tr>
<tr>
<td>MSAH</td>
<td>Ministry of Social Affairs and Health</td>
</tr>
<tr>
<td>NCC MERP</td>
<td>National Coordinating Council for Medication Error Reporting and Prevention</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroid Anti-inflammatory Drugs</td>
</tr>
</tbody>
</table>
OR  Odds Ratio
SD  Standard Deviation
WHO  World Health Organization
List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


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1 Introduction

The risk for medication-related adverse events is present every time medicines are administered. Consequently, for long pharmacological care has been characterized by careful assessment of risk and benefit. Research from previous decades has, however, demonstrated that medication-related harm is a significant problem causing patient harm by increased morbidity and mortality (Alhawassi, Krass, Bajorek, & Pont, 2014; Krähenbühl-Melcher et al., 2007; Panagioti et al., 2019). It has been estimated that adverse drug events affect approximately one fifth of all inpatients and cause 2-5% of unplanned hospitalizations in the adult population (Alhawassi et al., 2014; Bouvy, De Bruin, & Koopmanschap, 2015; Juntti-Patinen, Kuitunen, Pere, & Neuvonen, 2006; Pedrós et al., 2014). Thus, besides patient harm, medication-related adverse events inflict significant costs and functional challenges to health care organizations worldwide (Walsh et al., 2017). Although medication-related harm can occur in all age groups, geriatric patients are known to have higher susceptibility to harm caused by medicines (Mangoni & Jackson, 2004).

Medication-related adverse events can be categorized into adverse drug events (ADEs) and medication errors (MEs). ADEs include direct pharmacological reactions, such as bleeding due to excess anticoagulation, as well as indirect events such as falling due to vertigo caused by blood pressure medication. MEs, on the other hand, are errors and mishaps that can occur anywhere in the medication process from prescribing to dispensing thus resulting in ADEs unless interrupted. Consequently, in order to form a comprehensive understanding of the problem of medication-related harm, focusing on just one type of event is not enough. Moreover, understanding the association between different types of medication-related adverse events is important as ADEs resulting from MEs are considered preventable: approximately 30% of all detected ADEs could be prevented by preventing the causative error in the medication process (IV, Alhawassi et al., 2014). Therefore, to facilitate the development of safe and effective care, a complete overview of all occurring events is needed.

Research focusing on medication-related adverse events is important in improving both medication safety and patient safety. Besides facilitating the detection of any post-marketing ADEs in patient groups not included in clinical trials, it has significant implications in the assessment and development of national guidelines towards safer care. In addition to improving the overall detection of events, it also provides novel approaches for even prevention.
The main objective of this research project was to form a conclusive overview of the current situation of medication-related adverse events around the Finnish tertiary care units by including both medication errors and adverse drug events. The research project aimed to describe the frequency of in-hospital adverse drug events (I) as well as the prevalence of process-based medication errors (II, III) in an in-hospital setting, but also discover the extent to which outpatient ADEs burden tertiary care units by causing unplanned hospitalizations in the geriatric population (IV). Furthermore, the individual studies were designed to obtain information on population-based, medicine-based, and process-based risk factors for providing possibilities for nationwide improvements in patient safety during hospital care.

To provide a comprehensive overview of the research objectives, the data used in this study comprised of both real-world data (electronic health records from university hospital, data from the national register for patient safety incident reports) as well as data from electronic databases. In the description and analysis, both qualitative and quantitative methods were used to extract novel information about medication errors and adverse drug events. The research project was conducted in collaboration between the University of Oulu and Oulu University Hospital. It reflects the national need for patient safety research in Finland but also the local development strives in the hospital district of Northern Ostrobothnia during the time of this research project.
2 Review of the literature

2.1 Types and associations of medication-related adverse events

The tracking and analysis of counter effects of medicines started in the beginning of the 20th century in several western countries (Talbot & Aronson, 2012). At the time, the untoward effects were simply described as “side effects” of drugs. As both research and pharmacological understanding of these events grew, more specific definitions were needed. To date, the terminology in this field of research has, however, been highly heterogeneous.

The current terms used to describe medicine-related adverse events are adverse drug event (ADE), adverse drug reaction (ADR), and medication error (ME). There are several definitions available for these terms, but in this research project an ADR was defined according to the World Health Organization (WHO) as noxious or unintended response to a drug occurring at doses normally used in man for the prophylaxis, diagnosis, or therapy of a disease, or for modification of physiological function (World Health Organization, 2002). Similarly, there are multiple options available for defining an ADE. For this research project, the definition by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) and the Institute of Medicine (IOM) was selected, and an ADE was defined as an injury resulting from medical intervention related to a drug (Becker, 2015).

Although sometimes confused with each other, these terms describe events that differ both pharmacologically and phenomenologically; an ADR is a reaction that is usually directly attributable to the pharmacology of the causative drug whereas with ADE this is not necessarily the case. For example, a gastric ulcer caused by NSAID is considered an ADR because the pathogenesis is directly linked to the pharmacology of the NSAID. In turn, if a patient using benzodiazepines falls and is injured due to dizziness caused by the benzodiazepine, the injury caused by the falling is considered an ADE although falling itself is not linked to the pharmacology of benzodiazepine. In other words: An ADR is an effect that is created by a drug and an ADE is how a patient reacts to that effect (Talbot & Aronson, 2012). Furthermore, all ADRs are ADEs but all ADEs cannot be categorized as ADRs.

Although not always directly linked to patient harm, MEs are an important type of medication-related adverse events. The definition used for ME in this thesis was
written by Ferner and Aronson, and describes MEs as “A failure in the treatment process that leads to, or has the potential to lead to, harm to the patient” (Ferner & Aronson, 2006). According to this definition, MEs are errors, failures, and mishaps which occur somewhere in the medicine logistics, prescribing, handling, administering, or dispensing, and have the potential to cause ADEs or ADRs if left uninterrupted. Accordingly, MEs are generally used to divide ADEs and ADRs into preventable and unpreventable: an ADE or ADR caused by ME is considered preventable, whereas an ADE or an ADR occurring independently is not (Becker, 2015). Understanding the interplay of each event is critically important in both research and prevention of unwanted events. The relationship of ADE, ADR, and ME are illustrated in Figure 1.

![Fig. 1. The relationship between different types of medication-related adverse events.](image)

2.2 Assessing medication-related adverse events

Whenever it is suspected that patient harm was caused by a drug, two fundamental steps should follow: first, establishing potential causality and, after that, defining the degree of harm caused, i.e. the seriousness of the event.
2.2.1 Causality between a drug and adverse event

Only a small number of adverse events can be considered drug-related without alternative explanations (Figure 2) (Talbot & Aronson, 2012). In the majority of events, the causality between a certain incident and a medicine must be assessed due to the non-specific nature of the event or reaction. In causality assessment, the probability of a certain drug and an ADR or an ADE is established.

![Diagram of causality assessment](image)

Fig. 2. Definitive ADRs that do not require specific causality assessment.

Typically, ADRs are categorized into type A and B reactions according to their pharmacology (Talbot & Aronson, 2012). Type A reactions are exaggerated effects that are pharmacologically typical to the specific substance. These reactions are generally easier to identify as they can be expected to occur in association with the drug. The majority of ADRs in the hospital setting or causing an admission to a hospital are considered to be type A reactions (Pirmohamed, Breckenridge, Kitteringham, & Park, 1998). These ADRs are potentially avoidable and often predictable. Type B reactions, on the other hand, are completely aberrant and cannot be connected to the known pharmacology of a drug. Type B reactions, unlike type A reactions, are also not dose-related. Therefore, both recognition and causality assessment of type B reactions can be difficult. Furthermore, the assessment can also be complicated by the time-dependency of the reaction: an ADR can occur time-dependently varying from immediate reactions to late and delayed reactions, or alternatively be completely independent of time, e.g. when administered amount changes due to altered pharmaceutical formulation.
Consequently, variation in the latency between drug intake and ADR adds the complexity of any assessment.

In addition to the features concerning ADEs and ADRs, there are several external factors that can affect the causality assessment. As the median age in society is increasing, ADEs and ADRs appear more commonly in patients with several medications and co-morbidities. This adds a number of variables to the causality assessment, such as alterations in physiological function and cognition, drug pharmacodynamics (e.g., receptor function, pharmacodynamic interactions), and pharmacokinetics (e.g., drug-drug interactions, changes in absorption). Thus, for regarding all aspects with as little bias as possible, multiple methods have been developed to establish reliable and repeatable assessments (Agbabiaka, Savović, & Ernst, 2008; Arimone et al., 2005).

Methods used for causality assessment can coarsely be divided into three categories: operational algorithms, expert judgement, and probabilistic approaches (Agbabiaka et al., 2008; Arimone et al., 2005). In the probabilistic approach, the epidemiological information of the ADR or ADE and the background of the present symptoms are combined into an estimate of causality. This is done by calculating the likelihood ratios for every relevant element of the case, then breaking them down into components applying to a specific category of case information, and, finally, the terms are multiplied by one another to obtain the probability of causality. The complex calculations allow simultaneous assessment of multiple causes with an unlimited amount of assessed case details. On the other hand, they also make the method strenuous and therefore unpopular in clinical use, which is why expert judgement and algorithms have been more widely used (Agbabiaka et al., 2008).

All algorithms developed for causality assessment share the basic structure: they are flow charts with step-by-step instructions on determining the probability of causation (Agbabiaka et al., 2008). They provide a systematic approach to detect ADEs and ADRs based on questions, such as time to onset, previous reactions to de-challenge or re-challenge, and pharmacological basis of the phenomenon. Examples of popular algorithms currently applied include the algorithm by the World Health Organization and Uppsala Monitoring Center (WHO-UMC) as well as the Naranjo algorithm (Gates, Baysari, Mumford, Raban, & Westbrook, 2019; Naranjo et al., 1981; The Uppsala Monitoring center, 1994). Despite structural similarities, all algorithms differ widely in the probability categories used. Studies have also shown poor inter-rater reliability (Macedo, Marques, Ribeiro, & Teixeira, 2003). Furthermore, clinical judgement is also often required at various stages to reach a conclusion in the assessment (Frick, Cohen, & Rovers, 1997). A preferred
algorithm for causality assessment has not been recommended. However, different algorithms are widely used as they have good usability on clinical practice and have a high degree of consistency and reproducibility (Agbabiaka et al., 2008).

The most common method for causality assessment is using an expert panel or a single expert, typically a physician or a pharmacist, in concluding the relationship between a drug and an adverse event (Agbabiaka et al., 2008). In this method, assessment of causality is reached by considering all available data relevant to the suspected incident, estimating their relative importance, and finally assigning weights to reach the probability of causation (Arimone et al., 2005). The assessment is entirely based on the knowledge of the expert and in previous research, low inter-rater agreement as well as poor reproducibility of assessments has been detected. However, due to its’ simplicity, this expert judgement is widely used in both clinical practice and research.

Although methods for causality assessment differ in many aspects, they all provide a structured way to approach causality assessment. Currently, the method selection is mainly determined by availability of event details. Regardless of the selected method, reaching a reliable estimate of the causality between adverse event and drug is the not only the cornerstone for pharmacovigilance but also the basis of all ongoing long-term safety assessment of medicines currently on the market.

2.2.2 The seriousness of event

When assessing medication-related adverse events, two questions arise: what the severity of the reaction was and to what extent did it cause patient harm, i.e. how serious was the event. Although often used interchangeably, seriousness and severity differ fundamentally regarding the features of events that they describe (Gates et al., 2019; Talbot & Aronson, 2012). For example, if a drug causes urine discoloration as an adverse effect, the severity i.e. the intensity, of this reaction can vary anywhere from minor discoloration to extremely prominent. However, the discoloration can be very severe without inflicting any harm to the patient. Thus, medication-related harm can simultaneously be described as severe but not necessarily serious. Although the majority of previous research has focused specifically on the seriousness of ADEs and MEs, a number of studies have referred to this as event severity (Gates et al., 2019). In this thesis, the extent of patient harm is referred to as seriousness of event.
It is widely accepted, that medication-related adverse events can inflict serious patient harm including fatality (Cousins, Gerrett, & Warner, 2012; De Boer, Kiewiet, et al., 2013). On the other hand, ADEs and MEs can also be rather harmless causing only minor consequences to the patient. This is especially true for MEs as they can be intercepted before reaching the patient and thus, despite posing inherent risk to patient safety, cause no actual harm. Accordingly, approximately 25-50% of ADEs and ADRs are estimated to cause serious harm to the patient (Clementi et al., 2014; Davies et al., 2010; De Boer et al., 2013; Viana et al., 2018). For MEs, the proportion of errors causing severe patient harm ranges from 0.9% to 9% (Beckett et al., 2012; Cousins et al., 2012; Sakowski et al., 2008; Thompson et al., 2015). This is further endorsed by Marshman et al. (2006), stating that only 2.8% of all MEs ever lead to actual ADEs (Marshman et al., 2006).

Due to the significant variation in event consequences, the assessment of event seriousness is important when evaluating the total impact of medication-related adverse events. In addition to the widely used expert-panel assessment, several tools have been developed for event categorization of both MEs and ADEs: in a recent review by Garfield et al. (2013), more than 40 different assessment tools were identified. A few examples of the most frequently used assessment tools are presented in Table 1 (Garfield et al., 2013; Gates et al., 2019; Goedecke et al., 2016; Hartwig et al., 1992). These tools usually provide criteria by which events are categorized into a hierarchy describing seriousness; typically, from no harm to fatal events. The tool by NCC MERP was initially developed for categorization of MEs, but has also been used for the assessment of ADEs as well (Seddon et al., 2013).

<table>
<thead>
<tr>
<th>NCC MERP</th>
<th>HAMEC</th>
<th>Dean and Barber</th>
<th>Hartwig and Siegel</th>
</tr>
</thead>
<tbody>
<tr>
<td>A No error, no harm</td>
<td>0 No harm</td>
<td>0-10</td>
<td>1 ADR, no change in treatment</td>
</tr>
<tr>
<td>B-D Error occurred but caused no harm</td>
<td>1 Minor harm</td>
<td>Where 0 represents no potential effect to patient and 10 represents an incident that will result in death</td>
<td>2 ADR required discontinuation of suspected drug, no antidote</td>
</tr>
<tr>
<td>E-H Error occurred causing harm to the patient</td>
<td>2 Moderate harm</td>
<td>3 ADR required discontinuation of treatment and antidote</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 Serious harm</td>
<td>4 ADR that increases LOS with at least 1 day or is the reason for admission</td>
<td></td>
</tr>
<tr>
<td>I Error occurred causing patient death</td>
<td>4 Severe harm</td>
<td>5 any level 4 ADR that required ICU care</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 ADR causes permanent harm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7a ADR indirectly linked to death</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7b ADR directly linked to death</td>
<td></td>
</tr>
</tbody>
</table>
Although all the tools developed share the basic concept of event hierarchy, the categories within each method differ significantly from one another. Thus, the comparison of assessments conducted with different methods is challenging (Garfield et al., 2013). Furthermore, several studies have also shown confusion in assessment of risk (the overall potential to harm) and outcome (the actual harm) (Gates et al., 2019). Similarly to causality assessment, there’s no selected standard for assessment of seriousness (Garfield et al., 2013). Nevertheless, including the assessment to individual studies is important as it increases the clinical significance of the research findings. Furthermore, it creates a concrete outcome for an event that can sometimes appear somewhat theoretical and should thus be encouraged in all event documentation. The importance of assessment of event seriousness is highlighted in studies III and IV in this research project.

2.3 The prevalence of in-hospital medication-related adverse events

Medical care today largely relies on the use of different drugs for both the treatment and diagnostics of several conditions. As ADEs, ADRs, and MEs can occur in any situation where medicines are used, they are detected in almost all health care settings (Alshehri et al., 2017; Asaad Assiri et al., 2018; Cullen et al., 1997). Accordingly, international awareness of the magnitude of medication-related adverse events has markedly grown over the past few decades (Panagioti et al., 2019). This awareness has resulted in estimates of approximately 200,000 annual fatalities in the EU and other western countries, placing ADEs and ADRs within the 10 most common causes of death in the developed countries (European Commission, 2008; Lazarou et al., 1998; Makary & Daniel, 2016; Wester et al., 2008). Furthermore, it is estimated that millions of patients are affected by these events annually, making medication-related adverse events as severe of an issue in health care as malaria or tuberculosis in the developing countries (Makary & Daniel, 2016).

Compared with the outpatient setting, in-hospital treatment can have a higher risk of adverse events due to more frequent use of drugs with a narrow therapeutic range, e.g. chemotherapeutic agents and general anesthetics (Khan, 2013). In-hospital treatment also often includes parenteral administration, e.g. intravenous administration or intrathecal administration, that have higher risk for complications such as injection site infection. Furthermore, intravenous administration of drugs
usually has a greater potential for harm as it bypasses many of the safety mechanisms present in oral administration. It is also well recognized that patients admitted to the hospital tend to have lowered physical condition, poorer body defense mechanisms, and are more frequently affected by polypharmacy making them even more susceptible to adverse effects of drugs compared to outpatients (Khan, 2013).

A number of studies have been conducted on hospital-acquired ADEs, ADRs, and MEs (Choi et al., 2016; Cullen et al., 1997; Davies et al., 2009a; Viana et al., 2018). In individual studies, the prevalence of ADE and ADR vary from 1.6% to 58% according to selected specialty, age group and event definition (Dequito et al., 2011; Hakkarainen et al., 2012). Furthermore, in some studies the interchangeable use of the terms ADE and ADR increases the heterogeneity and causes misinterpretations of the results (Nebeker et al., 2004).

Accordingly, the lack of consistency in the use of basic terminology as well as the differences in patient populations in various specialties complicate data abstraction, which can be seen in the estimates from a number of systematic reviews and meta-analyses concerning inpatient ADEs and ADRs (De Vries et al., 2008; Martins et al., 2014a; Miguel et al., 2012; Wolfe et al., 2018). A study by Martin, Giordani & Rozenfeld (2014) highlights the effect of detection methods used on the prevalence rates of medication-related adverse events. Depending on the method used, the calculated frequency for hospital-acquired ADEs and ADRs can vary from 2.3% to 21.3%, where the highest frequency is provided by prospective detection and the lowest by stimulated reporting (Martins et al., 2014). Again, in a meta-analysis with all ADEs, the prevalence was estimated 9.2% (de Vries, Ramrattan, Smorenburg, Gouma, & Boermeester, 2008). When ADRs are studied alone, the frequencies achieved by meta-analyses vary from 1.6% to 16.8% (Bouvy et al., 2015; Hakkarainen et al., 2012; Miguel et al., 2012).

In addition to ADEs and ADRs, in-hospital MEs are also highly frequent as medicines are prescribed, transcribed, dispensed, stored, distributed, and administered daily in almost every health care unit (World Health Organization, 2016). Again, results of individual studies show significant variation in error frequency depending on ME definition, error type, studied specialty, and detection methods (Alshehri et al., 2017; Keers et al., 2013b; Krähenbühl-Melcher et al., 2007; McLeod et al., 2014). In a review by Keers et al. (2014), the overall prevalence of MEs in adult inpatients was 19.6%. However, in different care settings and patient populations the prevalence has varied from 6.3% in pediatric patients to 22.2% in surgical adult patients (Härkänen et al., 2015; Kaushal et al.,
In psychiatric patients ME prevalence has been detected varying from 10.6 to 17.5 errors per 1000 patient days and in ICU from 3.3% to 72.5% (Alshehri et al., 2017; Kiekkas et al., 2011). The prevalence of different medication-related adverse event types in various study settings and populations are presented in Table 2.

Table 2. The prevalence of medication-related adverse events.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Studied event (Definition)</th>
<th>Study setting, study population</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cullen et al. 1997</td>
<td>ADEs</td>
<td>prospective, ICU patients</td>
<td>19/1000 pd</td>
</tr>
<tr>
<td>Viana et al. 2018</td>
<td>ADEs (WHO)</td>
<td>Prospective, all adult patients</td>
<td>24.7%</td>
</tr>
<tr>
<td>De Boer et al. 2013</td>
<td>ADE (Morimoto)</td>
<td>Surgical patients</td>
<td>15.4%</td>
</tr>
<tr>
<td>Davies et al. 2009</td>
<td>ADR (Edwards &amp; Aronson)</td>
<td>Prospective, all patients from selected medical and surgical wards</td>
<td>14.7%</td>
</tr>
<tr>
<td>Dequito et al. 2011</td>
<td>“pADE is an adverse event related to both a drug and a ME”</td>
<td>Patients from geriatric, internal medicine and gastroenterology/rheumatology</td>
<td>58%</td>
</tr>
<tr>
<td>Kunac et al. 2009</td>
<td>ADE (“Actual injuries resulting from medical interventions”)</td>
<td>Prospective, paediatric patients</td>
<td>12.9/100 adm, 22.1/1000 pd</td>
</tr>
<tr>
<td>Choi et al. 2016</td>
<td>MEs (“Any preventable event that occurs in the process of ordering or delivering medication, regardless whether an injury occurred or the potential for injury was present”)</td>
<td>Case-Control, Voluntary error reports from selected hospitals</td>
<td>0.8/100 adm, 1.6/1000 pd</td>
</tr>
<tr>
<td>Thompson et al. 2009</td>
<td>Medication-related problems (“an event or circumstance involving drug treatment that actually or potentially interferes with the patient experiencing an optimum outcome of medical care”)</td>
<td>Prospective, obstetric and gynaecological patients patients with at least 1 medication-related problem</td>
<td>201/241</td>
</tr>
<tr>
<td>Urbina et al. 2014</td>
<td>Drug-related problems (“An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcome”)</td>
<td>Prospective, Cardiology patients</td>
<td>29.8%</td>
</tr>
</tbody>
</table>

Abbreviations: adm = admission, pd = patient days
Many of the studies focusing on the prevalence of medication-related adverse events have also researched the preventability of these events. (Cullen et al., 1997; Dequito et al., 2011; Fanikos et al., 2007; Hakkarainen et al., 2012; Marshman et al., 2006). Considering the high frequency of such events, the preventability of medication-related adverse events is of great importance to medication safety in health care. In previous research, the preventability ADEs varies between 13% to 87% with majority of studies estimating it between one third and half of all ADE cases (Giardina et al., 2018; Hakkarainen et al., 2012; Härkänen et al., 2015; Kanjanarat et al., 2003; Smith et al., 2006). In other words, errors in the medication process occur in a significant proportion of all ADEs, reinforcing the need for error prevention in all health care units.

2.3.1 Economic effects in health care

Medication-related adverse events cause major burden to health care systems by increasing morbidity and mortality (Bouvy et al., 2015). Accordingly, they also inflict significant economic consequences worldwide (European Comission, 2008; Giardina et al., 2018; Hoonhout et al., 2010). The total annual costs of all medication-related adverse events vary between different countries: In Europe, the costs reach €79 billion whereas in the USA they range from $76,6 billion to $177,4 billion (Bates et al., 1997; Ernst & Grizzle, n.d.; European Comission, 2008; Johnson & Bootman, 1995). The estimates largely depend on the selected event: in a recent review by Walsh et al. (2017), the costs arising from a single ME ranged from €2,58 to €1,117,08, where the lowest cost was associated with unnecessary immunization of children and the highest with litigation costs (Walsh et al., 2017). With ADEs and ADRs, the excess cost per event is estimated to range from $2262 to €7192 (Classen, Pestotnik, Evans, Lloyd, & Burke, 1997; Hoonhout et al., 2010; Marques, Penedones, Mendes, & Alves, 2016). Along with the event type, the costs related to an individual event are also closely connected to the seriousness of the incident. A life-threatening event will require additional treatment and surveillance that will rapidly increase expenses whereas for less serious events such actions are not needed. Furthermore, it has been suggested that the costs might differ between care settings, with slightly lower costs related to events in primary care compared to tertiary care (Walsh et al., 2017).

From an organizational perspective, the total cost related to MEs, ADEs, and ADRs consists of several event-specific factors as well as the stage of care process in which they occur (Davies et al., 2009; Walsh et al., 2017; Zhan & Miller, 2003).
In a study by Cullen et al. (1997), the costs of events related to intensive care were significantly higher than those related to non-intensive care (Cullen et al., 1997). Furthermore, Bates et al. (1997) found that the costs of preventable ADEs were 1.8-fold higher than those of non-preventable ones (Bates et al., 1997). It has also been shown that the related costs can vary between symptoms caused by the event, with the largest financial burden associated with fever, bleeding diarrhea, and cardiac arrhythmias (Classen et al., 1997).

In majority of studies, the direct costs of hospital-acquired events mainly consist of expenses related to length of stay, medication costs (e.g. additional treatments, exams, or medicines), and mortality (Davies et al., 2009a; Walsh et al., 2017; Zhan & Miller, 2003). Of these factors, length of stay is often highlighted as it, along with increased costs, causes significant functional challenges to health care units. Depending on the study, ADEs, ADRs, and MEs are estimated to increase the length of stay by 2 to 6 days, or 8.3% (Classen et al., 1997; Giardina et al., 2018; Hoonhout et al., 2010; Khan, 2013; Soop, Fryksmark, Köster, & Haglund, 2009). In addition to the direct costs, several indirect costs are associated with medication-related adverse events, such as outpatient care and sick leaves (Wu & Pantaleo, 2003). Indirect costs are often difficult to assess and are thus often not included in the estimates (Walsh et al., 2017; Wu & Pantaleo, 2003).

In addition to the costs inflicted by hospital-acquired events, ADEs and ADRs are a significant cause of unplanned hospitalizations (Oscanoa, Lizaraso, & Carvajal, 2017; Walsh et al., 2017). The estimates of unplanned hospitalizations due to medication-related adverse events vary from 2% to 5% in the overall population (Bouvy et al., 2015; Juntti-Patinen et al., 2006; Pedrós et al., 2014; Walsh, Lavan, Cushen, & Williams, 2015). When only geriatric patients are reviewed, the prevalence of medication-related hospitalizations is significantly higher. In a previously conducted review, the prevalence of unplanned hospitalizations of elderly patients varied from 5% to 46% with a mean prevalence of 11% (Alhawassi et al., 2014). Furthermore, in a recent review by Morabet et al. (2018) drug-related problems were found to increase hospital readmission by a median of 21% (El Morabet et al., 2018). As it is estimated that each ADR-related hospitalization causes approximately 5700 USD of additional costs, these visits have a significant impact on the health care economics (de Almeida et al., 2017).

The results received from economic studies tend to give conservative estimates on the total costs (Walsh et al., 2017). One reason for this is the limited number of parameters the studies use to measure economic impact of medication-related
adverse events. In addition, the events are often poorly recognized and therefore widely underreported, which is why it is difficult to accurately estimate the economic impact of medication-related adverse events (Milch et al., 2006; Nuckols, Bell, Liu, Paddock, & Hilborne, 2007). However, as the general population ages, it is evident that the economic weight of ADEs, ADRs, and MEs will increase. In countries with health care structures similar to Finland, this is expected to further stretch the already limited resources in the future.

2.4 Factors associated with in-hospital adverse events

The identification of factors increasing the susceptibility to ADEs and MEs has been the focus of interest in a number of previous studies as the knowledge of risk factors significantly improves the detection and prevention of medication-related adverse events (Alhawassi et al., 2014; Härkänen, Kervinen, et al., 2015). The effect of different variables on the medicinal outcome is presented in Figure 3. Here, the individual risk factors identified in previous research are grouped into 3 categories: population based, medication-based, and process based.

Fig. 3. Risk factors with a potential to affect medication outcome. LASA = Look Alike, Sound Alike -medicines.
2.4.1 Population based risk factors

It is widely acknowledged that inherent differences between individual patients exist in both therapeutic effect and probability of ADEs (Canet & Cherrington, 2014; Mangoni & Jackson, 2004; Notenboom et al., 2014). Within the past 20 years, the relationship between genotype and inter-individual variation in drug response has been established (Sim, Kacevska, & Ingelman-Sundberg, 2013). We now know that different genetic polymorphisms can affect the ADME properties of certain drugs and thus cause variation in both the efficacy and toxicity. Typically, the genetic variations occur in genes mediating either the metabolism or excretion of a drug, resulting in effects anywhere from lowered response to fatal toxicity of substances. Genetic factors are not, however, the only properties that can cause alterations in the ADME processes of an individual patient: several conditions, congenital or later developed, can significantly affect the use of medicines and increasing the risk for medication-related adverse events (Canet & Cherrington, 2014). Here, they are called the population-based risk factors.

Of all population based risk factors, higher age has one of the strongest and most consistent evidence of significantly increasing the susceptibility for both ADEs and MEs (Alhawassi et al., 2014; Asaad Assiri et al., 2018; Härkänen, Vehviläinen-Julkunen, Murrells, Rafferty, & Franklin, 2018; Hoonhout et al., 2010; Krähenbühl-Melcher et al., 2007; Sánchez Muñoz-Torrero et al., 2010). It has been estimated, that ADEs are up to 4 times more common in the elderly than in the general population with in-hospital events estimated to occur in 11.5% of the elderly patients (Alhawassi et al., 2014; Beijer & de Blaey, 2002). In addition, previous studies show that 10-30% of unplanned hospitalizations of the elderly are caused by medication-related adverse events (Alhawassi et al., 2014; Beijer & de Blaey, 2002; Hohl, Dankoff, Colacone, & Afilalo, 2001; Oscanoa et al., 2017).

Over the years, the understanding of the increase in susceptibility to ADEs in the elderly has grown markedly. It is now acknowledged, that the issue with increased risk and age is a result of multiple interconnected causes including alterations in both pharmacodynamics and pharmacokinetics, increased complexity of comorbidities, and simultaneous use of multiple medicines, i.e. polypharmacy (Alhawassi et al., 2014; Bénard-Laribièere, Miremont-Salamé, Pérault-Pochat, Noize, & Haramburu, 2015; Mangoni & Jackson, 2004). Pharmacodynamic and pharmacokinetic changes detected with increased age mainly result from changes in body mass distribution, lowered renal function, lowered metabolic capacity,
alterations in blood protein levels as well as changes in the function of several cell receptors controlling variety of basic body functions (Mangoni & Jackson, 2004). These changes can have drastic effects on medication use, making it a challenge to predict the effects of even commonly used medicines in elderly patients. In addition, the same physiological changes also increase frailty and comorbidities which are also independently linked to greater risk of ADEs (Notenboom et al., 2014).

Increased morbidity typically results in polypharmacy, as many of the common health issues today are effectively treated with medications. Polypharmacy has been connected to an increased risk of ADEs and MEs regardless of age group studied (Alhawassi et al., 2014; Asaad Assiri et al., 2018; Härkänen et al., 2018). This partly results from the higher error potential linked to a more complex medication regimen, but also from the increased likelihood for drug-drug-interactions (DDI), and potential overlapping of the pharmacology of medicines (Alhawassi et al., 2014; Mangoni & Jackson, 2004). Polypharmacy is highly common affecting approximately 58% of patients over the age of 65 and up to 70% of patients in nursing homes (Coiuti, Arnoldo, Cattani, Brusafyro, & Pea, 2016). To minimize medication-related harm, regular medication evaluations are recommended especially for patients with polypharmacy (Triantafyldis, Hawley, Perry, & Paik, 2018; Wawruc, 2008).

Decreased renal secretion and liver function have also been identified as ADE risk factors both as a part of ageing and as an independent condition (Krähénbühl-Melcher et al., 2007; Sánchez Muñoz-Torrero et al., 2010; Takahashi, Sakuma, Murayama, & Morimoto, 2018). Both liver and kidney diseases have great clinical significance as they can rapidly alter the metabolism and disposition of drugs (Canet & Cherrington, 2014). Decreased renal clearance can lead to drug accumulation, especially with medicines mainly eliminated in urine (Dresden, Allen, & Lyden, 2018). Renal function will decrease with age and should be regarded with dose adjustments in the elderly. However, especially quickly developing kidney diseases can have unexpected and severe consequences to pharmacological care.

The impact of hepatic dysfunction is less straightforward: the influence of decreased liver function can vary significantly even when drugs with the same metabolic pathway are taken (Westphal & Brogard, 1997). Furthermore, the effect of liver diseases is also complicated by their secondary effects on renal function. As with kidneys, age-related decrease also occurs in liver function (Tan, Eastment, Poudel, & Hubbard, 2015). Although liver dysfunction has the potential to cause
serious adverse effects, in the majority of cases it will not have as dramatic effect to drug disposition as kidney dysfunction (Diep, Chudow, & Sunjic, 2017).

Pediatric patients are also considered a special patient group particularly susceptible to ADEs and MEs. This is partly due to specific physiological features that must be addressed when treating children, but also to the common off-label use of medicines in this patient group (Turner, Longworth, Nunn, & Choonara, 1998). However, pediatric patients show lower number of medication-related hospitalizations than adults, with variation from 0.4% to 10.3% and a pooled estimate of 2.9% (Smyth et al., 2012). As with adult patients, the likelihood of ADEs and MEs is also significantly increased in children with polypharmacy (Lombardi et al., 2018).

Several studies have also suggested that female sex increases the risk for ADEs (Alhawassi et al., 2014; Asaad Assiri et al., 2018; Krähenbühl-Melcher et al., 2007). The causality is not, however, conclusively proven across studies (Härkänen, Ahonen, Kervinen, Turunen, & Vehviläinen-Julkunen, 2015; Pedrós et al., 2014; Sánchez Muñoz-Torrero et al., 2010). In a systematic review by Alhawassi et al. (2014), it was discussed whether the association between female sex and increased number of medication-related adverse events truly resulted from gender itself or rather from increased polypharmacy discovered in female patients.

For controlling the population based risk factors, specifically higher age, several methods have been developed to guide physicians to avoid prescribing potentially unsuitable medications. The STOPP (Screening Tool of Older Persons’ Prescriptions) and IPET (Inappropriate Prescribing in the Elderly Tool) are examples of such guidelines (Gallagher, Ryan, Byrne, Kennedy, & O’Mahony, 2008; Naugler, Brymer, Stolee, & Arcese, 2000). The tools aim to alert prescribers to more cautious use of certain medicines in patient populations more prone for adverse events. The clinical validity of such lists appears moderate, and their use is encouraged by several organizations and associations in the field (“American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults,” 2019; Gallagher et al., 2008; Wang-Hansen, Wyller, Hvidsten, & Kersten, 2019).

### 2.4.2 Medication based risk factors

In addition to population based risk factors, patients’ risk for ADEs and MEs is also influenced by the selection of drugs used in the treatment process (Zegers et al., 2018).
This is due to the diversity of the risk profiles within medicines: typically, a drug is considered high-risk when it has narrow therapeutic range or if it has a reported history of verified severe ADEs (Sheikh, Dhingra-Kumar, Kelley, Kieny, & Donaldson, 2017). Accordingly, drugs with a heightened risk of patient harm require additional attention as any error in their use can lead to severe consequences for the patient (Institute for Safe Medication Practices, 2018). Although the pharmacology of an individual drug predicts a great deal of the risk potential, the risk can also be heightened due to specific formulations, e.g. depot preparations, intrathecal preparations, or care situation they are used in (Institute for Safe Medication Practices, 2018).

Many international organizations have independently identified high-risk medications (Institute for Safe Medication Practices, 2018; NHS Specialist Pharmacy Service, 2017; Saedder, Brock, Nielsen, Bonnerup, & Lisby, 2014). In addition, the identification of high-risk medicines has also been the focus of several studies during the last decade (Franke, Woods, & Holl, 2009; Saedder et al., 2014; Tyynismaa, Honkala, Airaksinen, Shermock, & Lehtonen, 2017). The identification process is typically based either on error reports from health care organizations or prospective surveillance of errors (Franke et al., 2009). As a result, several high-risk medication lists have been created for different clinical care situations, e.g. ambulatory care, acute care, and long-term care (Institute for Safe Medication Practices, 2011a, 2011b, 2018). Furthermore, individual high-risk medication listings for different health care organizations are encouraged as this list can differ significantly according to the function and services provided by each unit and organization (Federico, 2007).

The medicines typically defined as having a high-risk in an inpatient setting are presented in Table 3. Clear similarities are seen in all listings indicating a strong evidence of the high-risk nature of the included drugs or drug classes. Furthermore, similar results can be seen in individual studies: In adult patients, medicines typically involved in ADEs and MEs include anticoagulants, heparins, NSAIDs, antibacterials, diuretics, beta blocking agents, chemotherapeutics, opioids and psycholeptics (Alhawassi et al., 2014; Hohl et al., 2001; Lapatto-Reiniluoto, Patinen, Niemi, Backman, & Neuvonen, 2015; Wolfe et al., 2018). There are no significant differences in high-risk medicines lists for pediatric inpatients when compared to that of adults (Maaskant et al., 2013). However, these lists are not conclusive but rather directive, as they fail to take into account many special features of different units and organizations. In Finland, the official high-risk medicine lists are lacking, but some recommendations have been made for certain
medicines and medicine groups that are frequently involved in patient harm (Inkinen & Volmanen, 2015).

Table 3. High-risk medicines listed by different organizations.

<table>
<thead>
<tr>
<th>Acute care</th>
<th>Long-term care</th>
<th>In-hospital</th>
<th>In-hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants, parenteral and oral</td>
<td>Anticoagulants, parenteral and oral</td>
<td>A PINCH:</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Chemotherapeutic agents, parenteral and oral (excl. hormonal agents)</td>
<td>Chemotherapeutic agents, parenteral and oral (excl. hormonal agents)</td>
<td>Anti-infective</td>
<td>Diamorphine and morphine injections</td>
</tr>
<tr>
<td>Hypoglycemics, oral (incl. combination products)</td>
<td>Hypoglycemics, oral (incl. combination products)</td>
<td>Chemotherapeutic agents</td>
<td>Liquid medicines</td>
</tr>
<tr>
<td>Insulins, all formulations and strengths</td>
<td>Insulins, all formulations and strengths</td>
<td>Heparin and Potassium and other electrolytes</td>
<td>Injectable medicines</td>
</tr>
<tr>
<td>Opioids, parenteral, transdermal, and oral preparations</td>
<td>Opioids, parenteral, transdermal, and oral preparations</td>
<td>Methotrexate</td>
<td>Vaccine cold</td>
</tr>
<tr>
<td>Liquid medicines</td>
<td>Injectable medicines</td>
<td>Methotrexate</td>
<td>Vaccine cold</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Injectable medicines</td>
<td>Methotrexate</td>
<td>Vaccine cold</td>
</tr>
</tbody>
</table>

Besides pharmacological and formulation-based problems, medication-related adverse events are also more frequent with pharmaceutical preparations that are confused with each other due to look-alike, sound-alike (LASA) features (Emmerton & Rizk, 2012). More precisely, LASA medicines are typically confused with each other due to similar packaging, similar-sounding product name, or active substance name. Throughout the literature, LASA errors have been linked to an increased patient morbidity and mortality (Basco, Ebeling, Hulsey, & Simpson, 2010; Ciociano & Bagnasco, 2014). It has been estimated that they account for up to 58% of all ME in the US (Berman, 2004). Although the pharmaceutical industry has taken actions to prevent the formation of new LASA pairs, the problem with LASA errors has grown markedly with the rapid increase of marketed medications. Furthermore, LASA errors are highly unit-specific, which is why they cannot be listed in high-alert medication lists as it is done with other generalized medication groups.
Several prescribing guidelines have been created to manage the prescribing of potentially high-risk preparations. These include START (Screening Tool Alert Doctors to Right Prescribing), Beers criteria, and MAI (Medication Appropriateness Index) (Barry, Gallagher, Ryan, & O’mahony, 2007; Beers et al., 1991; Hanlon et al., 1992). Although prescribing guidelines do provide valuable help, none of the methods have been selected for more generalized use in clinical practice.

2.4.3 Process based risk factors

Throughout the medication process there are factors that can affect medical care and result in patient harm. Typically, these events are unintentional errors and mishaps, e.g. medication errors. Whenever a ME results in an ADE, the ADE is considered preventable. Thus, there has been a great international interest in identifying high-risk situations more prone for mistakes, as this might decrease the amount of ADEs roughly in half (Hakkarainen et al., 2012; Wolfe et al., 2018).

The in-hospital medication process includes describing, distribution, storing, handling, preparing, dispensing, and administering medicines. In contrast to the outpatient setting, in-hospital prescriptions can either be written or verbal, and many times include transcribing to the electronic patient records (EHR) by either pharmacists or nursing personnel. Another typical feature of in-hospital medication is that it is often executed by multiple people at different stages of the medication process, but also between staff shifts and different courses of treatment. During admission, patients can also be transferred from one unit to another, which requires effective transfer of detailed medication information. Furthermore, in health care units, medical treatment can be implemented via several routes of administration that are impossible to use in outpatient care and that are also generally considered high-risk.

MEs occur most frequently during administration and prescribing (Asaad Assiri et al., 2018; Keers, Williams, Cooke, & Ashcroft, 2013a; Kopp, Erstad, Allen, Theodorou, & Priestley, 2006; M. McLeod et al., 2014). It is estimated, that 7% of all prescriptions contain errors, which is typically a result of inappropriate prescribing or prescribing a wrong dose (Asaad Assiri et al., 2018; Barry et al., 2007; Lewis et al., 2009; Passarelli, Jacob-Filho, & Figueras, 2005). Inappropriate prescribing affects 58% of elderly patients and accounts for 25% of ADRs (Barry et al., 2007; Passarelli et al., 2005). In a study by Krähenbül-Melcher et al. (2007), high workload, IT-shortcomings, complex polypharmacy, and physician
inexperience were all found to increase the likelihood of prescribing errors (Krähenbühl-Melcher et al., 2007).

Administration errors have been estimated to occur in 19.1% of total opportunities for errors (M. C. McLeod, Barber, & Franklin, 2013). Approximately half of these errors occur during the administration of intravenous drugs (Keers et al., 2013b; M. McLeod et al., 2014; Taxis & Barber, 2003). Alarming, administration stage MEs are also the errors least likely to be intercepted before affecting the patient (Leape et al., 1995). Accordingly, among all MEs, administration errors are linked to the highest number of severe and fatal ADEs (Cousins et al., 2012). Inadequate written communication, problems with medication supply and storage, high workload, problems with ward-based equipment, and interruptions or distractions have all been identified as predisposing factors to administration errors (Keers, Williams, Cooke, Walsh, & Ashcroft, 2014).

Although administration and prescribing errors are consistently the most frequently reported error types, errors do occur to a lesser extent in all other process stages. Choi et al. (2016) discovered a high prevalence of transcribing errors (25.7%), dispensing errors (18.5%), and ordering errors (15.5%). Dispensing errors are estimated to occur in approximately 2% of all dispensed drugs (Beso, Franklin, & Barber, 2005). In addition, in a study by Ben-Yehuda et al. (2011), transcribing errors were found to be nearly as common as prescribing errors.

Aside from errors occurring at various stages of medication process, there are also specific situations during treatment that will significantly increase the risk for MEs. Bobb et al. (2004) found that 64% of MEs occur at the time of admission to the hospital. It has also been shown that 50% of MEs occur within 3 days of hospital admission, highlighting that the beginning of hospitalization is especially prone to cause medication-related adverse events (Ben-Yehuda et al., 2011). This is further emphasized by results of several studies showing major discrepancies in patients’ medication regimen in up to 60% of patients during admission (Cornish et al., 2005; Lau, Florax, Porsius, & De Boer, 2000; van Doormaal et al., 2009).

The important role of care interfaces as a risk factor for ADEs and MEs is further endorsed as discrepancies with other medication-related problems have also been shown to frequently occur in patient transitions or handoffs between sites of care (Belda-Rustarazo et al., 2015; Boockvar et al., 2010; Breuker et al., 2017). In these stages, the most common error is the omission of drug from the patient’s medication regimen during both admission and discharge (Belda-Rustarazo et al., 2015). This most commonly arises from poor transfer of information. Attempts
have been made to tackle the errors at both admission and discharge: significant reduction of ADE-related readmissions (67%), ED visits (28%), and hospital readmissions (19%) have been seen after comprehensive medication reconciliation programs (Mekonnen, McLachlan, & Brien, 2016).

### 2.5 Surveillance of in-hospital medication-related adverse events

Detection of medication-related adverse events is a key element in medication safety: only event detection can provide means for prevention (Figure 4). Furthermore, this is a fundamental component of all pharmacovigilance and post-marketing surveillance as only a small proportion of adverse events related to drugs occur during clinical trials (Talbot & Aronson, 2012). The underlying reason to this is that clinical trials are typically conducted with small population of healthy subjects within a limited time span. As a result, the majority of rare ADEs and ADEs with a latency period only occur after marketing authorization as drugs are used for long-term in general population (Talbot & Aronson, 2012). Thus, detection of such events solely relies on long-term surveillance.

![Fig. 4. The association of description, detection, and prevention of medication-related adverse events.](image)

Medication-related adverse events are notorious for being under-detected (Milch et al., 2006). It has been estimated, that only approximately 3-10% of all medication-related adverse events are ever identified with the current methods (Classen et al., 2011; Cullen et al., 1995; Naessens et al., 2009; Tchijevitch, Nielsen, & Lisby, 2017). Currently, detection of medication-related adverse events relies on a variety
of methods that can broadly be divided into 3 categories: incident reporting, direct surveillance, and computerized monitoring (Manias, 2013; Thürmann, 2001). All three method types are widely used in research as well as in clinical practice. However, significant differences have been detected in event detection rates and types of detected events between all methods (Thürmann, 2001). Furthermore, these differences inevitably affect the drugs most frequently detected in ADEs and MEs, as well as ratios between preventable and unpreventable events reported with these methods. The key points on the advantages and limitations of each method type are presented in Table 4.

Table 4. Main classes of detection methods for medication-related adverse events and most important advantages and disadvantages related to them.

<table>
<thead>
<tr>
<th>Method specifications</th>
<th>Incident reporting</th>
<th>Direct surveillance</th>
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<td>Examples of used methods</td>
<td>Voluntary reporting</td>
<td>Chart reviews</td>
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<td>Advantages</td>
<td>Claims data</td>
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<tr>
<td></td>
<td>Reports in structured form</td>
<td>Accurate</td>
<td>Multidata-source</td>
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<tr>
<td></td>
<td>Data is easily gathered and events</td>
<td>Captures active errors</td>
<td>integration</td>
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<tr>
<td></td>
<td>Promotes culture of safety</td>
<td>Wide impact</td>
<td>Real-time method</td>
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<tr>
<td></td>
<td></td>
<td>Good detection rates</td>
<td>Enables ADE prevention</td>
</tr>
<tr>
<td>Limitations</td>
<td>Underreporting</td>
<td>Costly</td>
<td>Inserted errors</td>
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<tr>
<td></td>
<td>Variable quality of reports</td>
<td>Time-consuming</td>
<td>Poor triggers</td>
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<tr>
<td></td>
<td>Blame culture</td>
<td></td>
<td>Alert fatigue</td>
</tr>
</tbody>
</table>

Abbreviations: GTT = Global trigger Tool

Incident reporting refers to the identification of medication-related adverse events where the detection occurs via independent report of each event (Manias, 2013). It can, thus, for example, be conducted as voluntary reporting by health care professionals or as claims data consisting of patient complaints (Montesi & Lechi, 2009). Regardless of the reporting arrangements, incident reporting provides retrospective data on the events. Furthermore, it is characterized by mainly detecting latent errors with potentially harmful outcomes and events causing only minor harm thus leaving more serious types of medication-related adverse events undetected (Milch et al., 2006; Nuckols et al., 2007; Tchijevitch et al., 2017).

The majority of health care organizations across the world have implemented different methods for voluntary reporting of medication-related adverse events (Milch et al., 2006). For long, it has been considered as a primary method for ADE and ME detection (T. Gandhi, Seder, & Bates, 2000). The reason for the popularity
of this method is largely due to the low costs related to it as well as the simplicity of the method. However, incident reporting also consistently shows more under-reporting than other methods available (Manias, 2013; Montesi & Lechi, 2009). Low event frequencies have been detected even when reporting has been encouraged among hospital staff (Montesi & Lechi, 2009). It is also impossible to reliably determine event frequency when using this method alone.

Direct surveillance of medication-related adverse events can be conducted as real-time chart reviews, patient interviews, or as prospective observations (Manias, 2013). It has been suggested that direct surveillance, chart review in particular, is the most precise way of detecting ADRs (Montesi & Lechi, 2009). Furthermore, direct observation is the only reliable way to detect administration errors in real-time. Accordingly, accurate identification of events requires comprehensive training of event reviewers (T. K. Gandhi et al., 2003).

When compared with incident reporting, direct surveillance is more sensitive in event detection (T. Gandhi et al., 2000; Manias, 2013; Milch et al., 2006; Montesi & Lechi, 2009; Thürmann, 2001). It also has valuable qualities in preciseness and ability to impact treatment and therefore medication safety throughout the execution. Thus, detection and prevention by prospective surveillance and patient interviews has been made a part of clinical pharmacy services worldwide incorporating both surveillance and prevention to the admission and discharge stages of hospital stay (Al-Hashar et al., 2018; Colombo, Aguiar, Lima, & Storpirtis, 2017; Rudall et al., 2017; Wang et al., 2015). Although the impact of this work has been internationally recognized, direct surveillance of ADEs and MEs has been hindered by its high costs and laboriousness (Montesi & Lechi, 2009).

Similarly to direct observation, computerized monitoring of medication-related adverse events provides a method for prospective, real-time surveillance of untoward events (T. Gandhi et al., 2000; Manias, 2013). In this method, triggers are created out of words, laboratory results, and images that could, when combined with each other, refer to an ADE or ME. Triggers can alert physicians or pharmacists to events or factors that might otherwise stay undetected and result in an ADE. Furthermore, when combined with machine learning, trigger tools can quite easily be evolved into Clinical Decision Support (CDS) tools with even greater predictive value of avoidable events. It should be remembered, however, that although computerized methods are able to combine various data sources to create sophisticated signals, they are only able to flag events which still need to be confirmed by experts (Molokhia, Tanna, & Bell, 2009).
Compared with direct observation, computerized monitoring offers possibilities of covering a larger number of patients on a hospital level as it is less labour-intensive (T. Gandhi et al., 2000). It provides significant improvement in event detection, as even 8-fold differences have been shown in event identification compared to incident reporting (D C Classen, Pestotnik, Evans, & Burke, 1991). Furthermore, computerized monitoring can also enhance the detection of less common ADRs and ADEs. However, the method is only as good as the triggers it works by: poor quality of triggers can result in either positive or negative error in detection rates affecting the overall reliability and effectiveness of the method (Montesi & Lechi, 2009).

2.5.1 Incident reporting in the Finnish health care

As with Australia, the United Kingdom, Denmark, and the United States, Finland has launched a nationwide medication safety incident reporting tool as a part of a larger group of patient safety incident reporting (Haipro). With Haipro, health care professionals and patients can report all medication-related adverse events detected during treatment (Rauhala A et al., 2018). In Finland, the development of medication safety incident reporting began in 2007 in collaboration between the Technical Research Centre of Finland (VTT) and the Finnish Medicines Agency (Fimea). In the beginning, the use of Haipro tool was limited to a few pilot units, but in 12 years its’ use has expanded to over 200 units in health care and social services, covering more than 144,000 professionals in the field.

The Haipro system is fairly similar to that of medication safety incident reporting systems elsewhere in the Western World: it is designed to collect voluntary reports of medication safety incidents, including ADEs, ADRs, actual MEs and potential MEs. The main purpose of the Haipro system and others alike is to collect real-world data on the occurrence of various events in order to enable organizational learning (T. Gandhi et al., 2000). Therefore, in addition to promoting active reporting, the Haipro system requires efficient abstraction and analysis of reported data to enable potential organizational changes in accordance to the reports.

Haipro reports consist of two types of data: categorical data on several reported variables and narrative data on the actual event. The analysis methods for categorical data are generally well established and available. The narrative data, on the other hand, is not as easily analyzed as to date effective protocols have been missing. Therefore, obtaining comprehensive analyses of the reports, within
organizations or from nationwide data, has proven difficult and requires further development.

Along with in-hospital surveillance with Haipro reports, health care professionals and patients are encouraged to report all suspected ADEs to Fimea as a part of the national pharmacovigilance in Finland. This system is entirely separate from the Haipro system, as Haipro reports are only handled within the health care organizations. Therefore, the reports received and analyzed in Fimea are currently the only active method used to continuously abstract nationwide information on medication-related adverse events, ADEs in particular. Although these reports include events from both the inpatient and outpatient setting, they are invaluable in forming a comprehensive insight into the problems with medicines currently used in the Finnish health care system.

2.5.2 Prospects for event detection

As a result of the IT revolution during the past decades, electronic health records (EHR) have emerged in all health care units. EHRs include all data created during clinical care: medication information, health status, imaging, and laboratory results. The production of all this information in an electronic form has generated new opportunities for abstracting new kinds of observational, experimental, and knowledge-based data for the use of pharmacovigilance (Harpaz, DuMochel, & Shah, 2016). The data from EHRs of large patient masses construct what is called Big data: a large volume of diverse, distributed, and dynamic data. Big data has revolutionized the possibilities for ADE detection providing numerous new opportunities for research. However, it is also characterized by major challenges arising from its’ size, complexity, and content (Lee & Chen, 2019).

As the rapidly changing age structure in the western societies is deemed to increase the burden of the health care systems all over the world, effective methods are needed to control and effectively utilize the simultaneously growing data flow. With this awareness, computerized detection methods have gained popularity within health care organizations as they remain the only method capable of tackling the issue of large patient volumes (T. Gandhi et al., 2000; Tchijeitich et al., 2017; van Puijenbroek, Diumont, & van Grootheest, 2003).

Besides the capacity to handle big data, computerized monitoring has been the focus of interest for its potential for event prevention. Real-time alerts from EHRs enable immediate actions for preventing patient harm. The rapid advances in computerized method development also allow more advanced work in event
prevention (Gao, Igata, Takeuchi, Sato, & Ikegaya, 2017; Lee & Chen, 2019; Meng, Jin, Yan, & Yang, 2019). Through different models, machine learning could provide means for predicting likely ADEs as well as identifying entirely new ones. In other words, trigger methods have the potential to work as a game changer shifting the emphasis from retrospective event analysis to event forecasting – something health care organizations have not had the means until now.

However, there are obstacles to overcome with both computerized methods and EHR data, e.g. unstructured text, abbreviations, misspelling, and acronyms (Wunnava et al., 2019). It should also be remembered, that none of the developed computer-based methods can fully automate the process from ADE detection to prevention. Instead, they still require a human aspect for reinforcing the trigger alert and executing further procedures for prevention. Furthermore, computerized methods cannot detect errors and events where no electronic data is available, e.g. administration, dispensing, and transitions of care. Thus, suggestions of incorporation of multiple methods have been made (T. Gandhi et al., 2000; Thürmann, 2001). For example, combining voluntary reporting and in-hospital trigger-based detection method could enable event identification in both real-time and retrospectively. It is also likely, that voluntary reporting and EHR data mining would pinpoint different types of problems in the medication process and therefore complement each other. However, for comprehensive detection of real-time administration errors and undocumented events, direct surveillance must be included as it is currently the only effective detection method for these events (T. Gandhi et al., 2000; Montesi & Lechi, 2009).

2.6 Actions to prevent medication-related harm

When looking back in recent history, a variety of examples can be found where unexpected effects of drugs have led to severe patient harm and resulted in product withdrawal (Onakpoya, Heneghan, & Aronson, 2016). One of the most tragic and notorious examples is that of Thalidomide in the 1960s. Several incidents can also be found from the 1990s and 2000s, such as Cisapride, Terfenadine, Cerivastatin, and Rofecoxib (Sahu, Yadav, Prasad, Roy, & Chandrakar, 2014). In the latter examples, the consequences may not have been as drastic as with Thalidomide, yet they have resulted in common demand from health care professionals and patients to improve methods for managing risks and safety concerns related to medicines (Talbot & Aronson, 2012).
To ensure patient safety and acceptable risk-benefit ratio for medicines, cooperation is required between pharmaceutical companies and regulatory authorities throughout the drug’s lifecycle. Furthermore, separate organizations have been founded to increase international harmonization of guidelines in medication safety (Talbot & Aronson, 2012). Such organizations include WHO’s International Drug Monitoring program and VigiBase managed in Uppsala Monitoring Center (UMC). In VigiBase, spontaneous reports of ADRs have been collected since 1978 from over 150 member countries. In addition to constant pharmacovigilance monitoring in UMC, WHO has launched the Third Global Patient Safety Challenge: Medication Without Harm in 2017 (World Health Organization, 2017). The goal of this program is to promote selected key points in medication safety, including e.g. early action in event prevention, facilitating national guidance and action plans towards high-risk factors in medication use, and increasing methods for improved patient awareness.

Other international organizations involved in harmonization of medication safety across countries are the Council for International Organizations of Medical Sciences (CIOMS) and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). CIOMS was founded by WHO and the United National Educational, Scientific and Cultural Organization (UNESCO) to work as advisory and guiding forum for new developments in biology and medicine. ICH, on the other hand, is a joint organization for regulatory authorities of the European Union, the United States, and Japan. The main goal of ICH is to form recommendations for improved harmonization in guidelines and requirements for product registration in order to create opportunities for more unified market in all three areas. Both organizations also give recommendations regarding safety aspects of the use of medicines and thus take an active part in medication safety work.

Although the contribution of non-profit organizations to pharmacovigilance and medication harmonization are valuable, they are not obligatory requirements to national authorities and health care organizations. Binding requirements are defined by national authorities within each country. In the European Union, general guidelines and medication safety framework is legislated by the European Council (European Medicines Agency, 2019). The European Council manages this work through Regulations and Directives that constitute the European law. All Regulations will cause immediate actions across all member states in the European Union and through mutual agreement in Iceland, Norway, and Liechtenstein. Directives, on the other hand, require implementation by national authorities in
each country and can thus take longer to put into action. Furthermore, with Directives, different interpretations and variations in the execution between member states are possible.

The European Medicines Agency (EMA) was established by Regulation in 1995 to protect and promote public and animal health through evaluation and supervision of medicines for human and veterinary use (EEC/2309/93). Since then, the EMA has taken several tasks in the medical field, e.g. issuing of marketing authorizations through centralized procedure, providing medical advice, and pharmacovigilance. The EMA also has an important role in constant coordination of medication safety activities inside the EU, working in close contact with national regulatory authorities, patients, and health care professionals. In 2012 along with pharmacovigilance legislation, The Pharmacovigilance Risk Assessment Committee (PRAC) was established within the EMA. This legislation was endorsed by the discovery of 197 000 deaths caused by ADE annually in the EU. Since then, PRAC has been responsible for assessing all aspects of risk management of medicines.

The EMA develops strategies for annual objectives but also for multiannual, long-term goals. Currently, long-term goals for 2019-2021 consist of four themes: Contributing to human health, contributing to animal health and human health in relation to veterinary medicines, optimizing the operation of EMA's network, and contributing to the global regulatory environment (European Medicines Agency, 2018). All themes consist of different areas in medicine where improvements are needed, e.g. antimicrobial resistance, and effective and efficient pharmacovigilance. All progress within the selected areas are reported annually.

Although the work in EMA covers all the major outlines of rules and regulations around medicines in the EU, there are several aspects of medication safety, monitoring, and development that are left to the national authorities of each member country. These include the development of treatment guidelines, controlling of the advertisement of medicines, pricing and local availability of medicines, and providing medical advice. In Finland, all such tasks are managed by the Ministry of Social Affairs and Health (MSAH), the National Institute for Health and Welfare, and the Finnish Medicines Agency, Fimea.
2.6.1 Patient safety work in Finland

Systematic efforts to improve patient safety and thus medication safety in Finland began in 2005 with the establishment of the national patient safety network by the Ministry of Social Affairs and Health (MSAH) (Airaksinen, Linden-Lahti, & Holmström, 2012). In 2009 this work was further structured and enhanced by the development of the first National Patient Safety Strategy 2009-2013 by MSAH (Ministry of Social Affairs and Health, 2009). The main goal of this was to promote the incorporation of patient safety and quality control into the basic function and structures of health care organizations. In the strategy, outlines for achieving this goal were set. It also made it obligatory for every health care unit to develop and execute the processes for internal reporting, monitoring, and handling of Patient Safety Incident Reports. Thus, in 2007, the patient safety incident reporting system (Haipro) was introduced for this purpose (Keistinen & Kinnunen, 2008).

Since then, this strategy has been updated and a new version, the National Patient Safety Strategy 2017-2021, was published. In this version, patient safety work has been extended to cover social services as well (Ministry of Social Affairs and Health, 2017). One of the key aspects of the newer strategy was to encourage learning from occurred events within the organizations via improved sharing of such information. In this strategy, the main goals to reach by 2021 are to achieve apparent patient and client safety in the health care structures and practical operations to ensure safe and effective services and to achieve a state where a patient or a client are equal and active parties in the health service process as well as in planning of it (Figure 5). The execution and implementation of the National Patient Safety Strategies is coordinated and implemented by The National Institute for Health and Welfare.

In 2006, the National Institute for Health and Welfare published guidelines for safe medical practices for all units in health care and social care. These guidelines, updated in 2015, set the standard for good practices ensuring medication safety in all care settings. Accordingly, the guidelines require each unit to develop a pharmacotherapy plan according to which all practices within that unit are executed.

The latest national initiatives for improved patient safety were made in 2016 as MSAH nominated a steering group for creating an Action Plan for Rational Pharmacotherapy (Ministry of Social Affairs and Health, 2018a). This was further accompanied with publication of Research Strategy for Rational Pharmacotherapy 2018-2022 (Ministry of Social Affairs and Health, 2018b). The main objective of these initiatives is to improve rational use of medicines, e.g. knowledge-based
management of pharmacotherapy and pharmaceutical services. The goal is to achieve a system where pharmacological care is managed as whole and is supported by sufficient research as part of the self-assessing organizational structure. The initiatives aim to develop a future health care that most of all relies on clear evidence-based, safe and effective pharmacotherapy.

Fig. 5. The patient safety goals set in the National Patient Safety Strategy by the year 2021. The objectives promoted in this research project are highlighted in the picture.

Much of the patient safety work in Finland is based on and endorsed by legislation, such as the Healthcare Act (1326/2010), the Social Welfare Act
(1301/2014), and the Act on Supporting the Functional Capacity of the Older Population and on Social and Health Services for Older Persons (980/2012). However, valuable contributions to this field is also made by the Finnish Society for Patient Safety (FSPS). Established in 2010, FSPS is a non-profit organization focusing on promoting patient safety in all aspects of medical care with special focus on patient-centered approaches. Furthermore, FSPS has a significant role in encouraging research in all patient safety. One of the most visible forms of the work by FSPS is the involvement and collaboration with MSAH in the development of the National Patient Safety Strategy.
3 Aims of the study

The aim of this study was to assemble a comprehensive view of medication-related adverse events occurring around tertiary care by describing the occurrence, nature, and related factors affecting the events. The study focused on creating a basis for better knowledge of hospital-acquired events and events leading to hospital treatment in order to expand the possibilities for prevention and patient safety improvements. The primary viewpoint in this study was on the Finnish health care system, although an international overview was presented as well. The specific objectives described by study questions were:

1. What kind of medication-related adverse events occur during hospital admission? What medicines are most commonly involved in them? (I)
2. What type of medication errors occur in the Finnish medication safety incident reports (Haipros) between 2007 and 2017? What medicine groups are most commonly involved in the reports? (II)
3. What is the ME outcome and risk related to medicines most commonly involved in tertiary care ME reports? (III)
4. What is the proportion of geriatric patients admitted to hospital due to adverse drug events? (IV)

The objectives were formed based on a national need for better understanding and knowledge of medication-related adverse events. The study questions also depict the medication safety improvement strives initiated in the hospital district of Northern Ostrobothnia during the time of this research project.
4 Materials and methods

4.1 Study design

This was a cross-sectional study describing medication-related adverse events from different viewpoints around tertiary care. The emphasis of the study was to describe the prevalence of MEs and ADEs in tertiary care as an international challenge (I) but also as a national problem compromising patient safety and causing significant economic burden and organizational challenges (II-IV). The study was conducted using a variety of qualitative and quantitative research methods and multiple data sources in order to form a more precise overview of medication-related adverse events in health care (Tashakkori & Teddlie, 2010).

The study consisted of two parts, where the first part concentrated on ADEs and MEs in the inpatient setting and the second part on ADEs in the outpatient setting (Figure 6). In the first part, ADEs and MEs were studied from both national (II, III) and international (I) perspectives using meta-analysis and register study methods. In the second part, ADEs leading to hospitalization were studied from a national viewpoint in a cross-sectional register study (IV). Together the two parts provided an overall picture of different types of medication-related adverse events in different phases of hospital care.

In all individual studies, the Anatomic Chemical Classification (ATC) system was used to categorize medicines. In this classification system, medicine are categorized into groups A (Alimentary Tract and Metabolism), B (Blood and Blood Forming Organs), C (Cardiovascular System), D (Dermatological Drugs), G (Genitourinary System and Reproductive Hormones), H (Systemic Hormonal Preparations, Excluding Reproductive Hormones and Insulins), J (Anti-infectives for Systemic Use), L (Antineoplastic and Immunomodulating Agents), M (Musculoskeletal System), N (Nervous System), P (Antiparasitic Products, Insecticides and Repellents), R (Respiratory System), S (Sensory System), and V (Various ATC Structures) according to both their chemical properties as well as their Anatomic pharmacological functions.
Fig. 6. Outline of the study project. Near miss = intercepted Medication Error.
4.2 Literature review and meta-analysis of in-hospital adverse drug events in the Western countries (I)

4.2.1 Study setting

The study was a systematic review and meta-analysis carried out according to the recommendations by the PRISMA statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The PRISMA statement consists of a 2-item checklist and a four-phase flow diagram, which are designed to improve reporting in both systematic reviews and meta-analyses. It aims to develop of more reliable research and guides the construction of articles that are easier to assess for publication bias. In this research, the PRISMA statement was used in both designing the study and presenting it in an article.

4.2.2 Data collection and analysis

An electronic search was conducted between January 2000 and November 2016 from four large databases, Cochrane database, MEDLINE, Web of Science, and Scopus. Search terms created for databases consisted of field-specific terminology on in-hospital ADEs and ADRs. The reference lists of relevant articles were also cross-checked for any additional articles for inclusion. Articles that were not written in English were not included. An information specialist was consulted in designing the data collection and creating the search terms to achieve results as accurate as possible. All duplicate articles were removed from the retrieved results. After this, clearly unsuitable articles were removed according to the title. The remaining articles were assessed for inclusion according to the predefined criteria presented in Table 5.

Table 5. Inclusion and exclusion criteria.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Specific exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>Commonly accepted definition for ADE/ADR</td>
<td>Study focused on a specific ADE/ADR</td>
</tr>
<tr>
<td>ADE/ADR prevalence reported</td>
<td>Study focused on ADEs/ADRs of a specific drug</td>
</tr>
<tr>
<td>Study conducted in adult inpatients</td>
<td>Primary objective not ADE/ADR identification</td>
</tr>
<tr>
<td>Study conducted in the Western world countries</td>
<td>Primary detection method based on disease codes</td>
</tr>
<tr>
<td>Study period between 2000 and 2016</td>
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</table>

Abbreviations: ADE = Adverse drug event, ADR = Adverse drug reaction, disease codes refer to e.g. ICD-10
The study design, data collection period, population characteristics, and studied event including its definition were retrieved from the included articles. Complementary information was requested from the authors of one article (Hoonhout et al., 2010). The number of ADEs and ADRs gathered represents the sum of definite, probable, or possible events, as reported in the original articles. The accuracy of the gathered information was controlled by an independent assessment performed by a second researcher.

The gathered data on ADE and ADR prevalence was presented with pooled descriptive statistics. A meta-analysis was also performed on the prevalence of ADE, ADR and inpatient death due to ADR. For the meta-analysis, random effects model was used due to the significant heterogeneity in the results of independent articles (Diggle P, Heagerty P, Liang K-Y, 2002). Heterogeneity in the articles was also described with $I^2$ statistics (0-100%), where 0% indicated no heterogeneity. The statistical significance of $I^2$ was tested with Chi square test.

### 4.3 Medication error studies from national data (II, IIII)

#### 4.3.1 Study settings

The studies here were a descriptive analysis (II) and a cross-sectional description (III) of in-hospital MEs and potential MEs in the Finnish tertiary care units. The studies characterized MEs in the tertiary care medication process from the beginning of data collection in 2007 to the beginning of the study in 2017 (II), and in more precision during 2017 (III). The data used in both studies was granted by the FSPS and consisted of medication safety incident reports collected with the Haipro system. In the first study (II), all tertiary care MEs and potential MEs collected throughout the 10-year study period were included in the analysis. In the second phase (III), a take of the data (medication safety incident reports from 2017 concerning MEs only) was selected for more precise analysis concerning TOP15 medicines from the 5 most common ATC groups abstracted from the data in the first phase study (II).

#### 4.3.2 Data processing

The medication safety incident reports include reports on MEs (events that reached the patient) and potential MEs (intercepted errors). They also contain both
categorical and narrative data. The narrative form included a description of the event and the medicines involved in the event. The categorical data contained descriptions of e.g. event type, patient outcome, risk category, contributing factors, and organizational outcome. The narrative data was given by the reporter, whereas the majority of the categorical data was filled out by the unit supervisor (the person handling the reports within the organization).

In both studies (II, III), data needed processing before any analysis could be conducted. First, the anonymity of the data was ensured. Second, the narrative data was separated from the categorical data and imported to QSR Nvivo 12 (©QSR Nvivo International Pty Ltd) software for further analysis. In the first phase (II), the reports were categorized according to ATC codes by medicines involved in the reports. The categorization was conducted by search terms created out of every brand name and active substance name currently on the Finnish market. Correct categorization was manually ensured for the active substances or brand names that occurred simultaneously in several different ATC categories. The abstracted information was then connected with the categorical data and national health care medication consumption numbers collected from the Finnish Medicines Agency (Fimea) for further analysis.

In the second phase (III), the previously created search terms were utilized for identifying medicines by ATC codes from the selected take of 2017 medication error reports. From the results, the TOP3 medicines from the 5 most common ATC groups identified in the first phase (II) were extracted. The extraction was done by searching the 3 active substance names that appeared most frequently. The 3 medicines from each ATC group were included by frequency in the reports only, regardless whether they were generic preparations or not. This was done in order to maintain the sensitivity of the method for the potential LASA preparations in the reports. All reports including the selected TOP15 medicines were selected for inductive content analysis, in which medicines were categorized accordingly into 5 ME outcome categories. The analysis was then combined with the categorical data (risk assessments) included in the reports.

4.3.3 Analysis of qualitative data - Inductive content analysis

Inductive content analysis was performed on the included 1447 reports in the second phase of the ME study (III) (Elo et al., 2014; Zhang & Wildemuth, 2009). The design of the content analysis is presented in Figure 7. The codes created out
of the event description in the reports were categorized twice in the analysis process in order to create 5 final ME outcome categories for the reported events.

![Diagram of data analysis process]

**Fig. 7. Process of data analysis in the second phase ME study (III).**

After the inductive content analysis, the reports were reanalyzed with risk assessments provided in the medication safety incident reports. In the statistical analysis, Pearson’s chi-square test was used to test the relationship between assessed risk, ME outcome, and the TOP15 medicines in the reports. OR was used to assess the association between ME outcomes, risk categories and the TOP15 medicines.
4.4 Register study of adverse drug events as a cause of hospitalizations in the elderly (IV)

4.4.1 Study setting

The study was conducted retrospectively using register data from 2014 emergency care (EC) patient records from Oulu University Hospital. Oulu University Hospital is a university hospital providing tertiary care for the entire Northern Finland. There are over 55 000 emergency visits to Oulu University Hospital each year. The study targeted ADEs and ADRs causing hospital admissions in elderly patients. Because electronic patient records were used, the study required study permission which was granted by the Regional Ethics Committee of the Northern Ostrobothnia Hospital district.

4.4.2 Data collection, causality assessment, and data analysis

Out of all emergency department visits of geriatric patients during 2014, 2.5% (290) were selected in this study according to systematic random selection. After selection, included admissions were tested for bias towards age, sex, specialty, and the month of emergency department admission. For each included admission, electronic patient records including full medication regimen and laboratory results were reviewed. Information about the patients’ demographics, medication, comorbidities, potential ADEs and ADRs, and reason for admission was gathered.

Each admission was assessed by a multi-disciplinary research team (specializations from pharmacy, clinical pharmacology, and health sciences) in order to identify potential ADEs and ADRs. In this assessment, databases such as Riskbase, Inxbase, and the geriatric medicine database managed by FIMEA were used to detect any DDIs and potential ADEs or ADRs. Although the assessment by the research team was considered definitive, a customized Naranjo scale was used as control method in this study (Naranjo et al., 1981). Each admission was categorized to probable, possible, or doubtful according to both the research team assessment and the customized Naranjo scale. The customized Naranjo scale points and assessment criteria of the research team is presented in further detail in Figure 8.
Fig. 8. Assessment criteria by research team and points from the customized Naranjo scale.

All gathered sociodemographic data and mean values were analyzed using t-tests or analysis of variance (ANOVA) with post-hoc Tukey test. The value of the association between certain variables and hospitalization was described by the odds ratio, which was presented with its’ 95% CI.
5 Results

5.1 In-hospital adverse drug events in the Western world (I)

From the electronic database search, a total of 1611 citations were found from which 1241 remained for the evaluation of inclusion after duplicate articles were removed. These articles were screened by titles and abstracts to exclude articles clearly unsuitable for this study. After this, predefined inclusion criteria was used for 270 full-text articles, and, of these, 14 were then included in the final analysis (Davies et al., 2009b; De Boer, Boeker, et al., 2013; Dequito et al., 2011; Härkänen, Kervinen, et al., 2015; Hoonhout et al., 2010; Hug et al., 2010; Kilbridge, Campbell, Cozart, & Mojarad, 2006; Lapatto-Reiniluoto et al., 2015; Pardo Cabello, González Contreras, Manzano Gamero, Gómez Jiménez, & Puche Cañas, 2009; Alfredo José Pardo Cabello et al., 2016; Rothschild et al., 2007; Sánchez Muñoz-Torrero et al., 2010; Seddon et al., 2013). The selection process of included articles and reasons for exclusions are presented in Figure 9.

Fig. 9. Data search and selection process. WW = Western World.
The study characteristics are presented in more detail in study I (Table 1 and Table 2). Due to several different assessment methods used in the articles, the event seriousness assessed for this research was conducted by merging criteria from several individual methods used in the included articles in 4 new categories (Table 6). The articles reporting FADRs were not included in the re-categorization because they only reported fatal events, i.e. the most serious event type.

Table 6. Created categories for assessed severity of inpatient ADEs and ADRs, and the percentages of categorized events.

<table>
<thead>
<tr>
<th>Created categories for seriousness of events</th>
<th>Description</th>
<th>Mean % of re-categorized events (MD, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>No harm caused to the patient, no intervention</td>
<td>71.1% (^1)</td>
</tr>
<tr>
<td></td>
<td>e.g. Hartwig scale 1, NCCMERP A-D</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>No permanent harm to the patient, intervention</td>
<td>56.9% ((63.5, 25.2))</td>
</tr>
<tr>
<td></td>
<td>e.g. Hartwig scale 2-3, NCCMERP E</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Significant harm to the patient, intervention</td>
<td>27.7% ((28.9, 15.1))</td>
</tr>
<tr>
<td></td>
<td>e.g. Hartwig scale 4-6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCCMERP F-H</td>
<td></td>
</tr>
<tr>
<td>Life-threatening or fatal</td>
<td>Patient required intensive care or event resulted</td>
<td>3.7% ((2.0, 4.9))</td>
</tr>
<tr>
<td></td>
<td>in patient death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Hartwig scale 7a-7b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCCMERP I</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Only one article reported minor events

The calculated percentages represent mean values calculated from individual articles included in the literature review and meta-analysis

The medicines involved in ADEs, ADRs, and FADRs were categorized according to ATC groups and are presented, with the reported event types, in Figure 10 (Davies et al., 2009b; De Boer, Boeker, et al., 2013; Dequito et al., 2011; Hoonhout et al., 2010; Hug et al., 2010; Rothschild et al., 2007; Sánchez Muñoz-Torrero et al., 2010; Seddon et al., 2013). The most common inpatient ADEs were central nervous system (CNS) events (dizziness, sedation, delirium) and renal dysfunction/electrolyte disturbances. ADRs were most often allergic reactions or hematological events (bleeding), and FADRs hematological events or renal dysfunction/electrolyte disturbances. The medicines most frequently involved in ADEs were from the ATC groups N (Nervous System) and C (Cardiovascular
For ADRs, the most common medicine groups were N (Nervous System) and J (Anti-infectives for Systemic Use), and for FADRs B (Blood and Blood Forming Organs) and N (Nervous System) for FADRs.

Fig. 10. Adverse events and medicines most commonly involved in ADEs, ADRs, and FADRs. n(medicines involved in ADEs)=1865, n(medicines involved in ADRs) = 851, n(Medicines involved in FADRs)=217. n(ADEs) = 2427, n(ADRs = 121, n(FADRs) = 181.

Altogether 9 articles encompassing 46 626 patient visits to hospital reported the amount of ADEs in inpatients. The mean prevalence of inpatient ADEs was 21.6% (MD 19.7, SD 16.7) with significant variation between individual articles (from 61
1.9% to 57.9%). The pooled estimate (19%) calculated for the prevalence of ADEs also reflected the high heterogeneity in the results with an $I^2$ value of 99.49 (Figure 11). The mean value for preventable ADEs was 32.3% (MS 29.6, SD 22.6) varying from 12.0% to 75.0%. The mean value of ADR prevalence for the 2 articles reporting inpatient ADRs, with a total of 3727 patients, was 23.4% (SD 10.8) and only one article reported the number of preventable ADRs (53.3%). For FADRS, the mean prevalence abstracted from the articles encompassing 3385 patients, was 9.6% (SD 7.7) with variation from 4.5% to 18.4%. Due to a low number of included studies, the estimates for FADRs and ADRs were not reported.

Several factors were associated with a higher probability for inpatient ADEs and ADRs (Davies et al., 2009b; de Vries et al., 2008; Dequito et al., 2011; Härkänen, Kervinen et al., 2015; Hug et al., 2010; Sánchez Muñoz-Torrero et al., 2010; Seddon et al., 2013). In four articles, the risk of ADEs was associated with an increased length of stay. In 3 articles, there was a positive correlation between ADEs and higher age of patients. Furthermore, in 2 articles the risk of an ADE increased with polypharmacy, multimorbidity, and cardiovascular comorbidities. Other associated factors reported were vascular surgery, female gender, Caucasian race, decreased renal function, and any interaction in current medication. In two studies, FADRs were associated with polypharmacy (AJ Pardo Cabello et al., 2009;
Alfredo José Pardo Cabello et al., 2016). Other factors found to increase the risk of FADRs were multimorbidity and the presence of NSAID or antiaggregants together or alone in the medication regimen.

5.2 Medication errors in the Finnish tertiary care units and medicine-specific outcome of medicines most frequently involved in the reports (II, III)

In the first phase (II), all medication safety incident reports from July 2007 to July 2017 were processed for analysis. The collected 10-year data consisted of 369,739 medication safety incident reports. Of these reports, 90,352 were from tertiary care units and were included in the analysis. Reports on MEs covered 58.8% of the reports with the remaining 41.5% describing potential MEs. The majority (89.9%) of the reports were made by nursing personnel, 4.6% by pharmacists, 2.2% by physicians, and 0.1% by other than staff members (patients or relatives).

The search method created for detecting medicines in the reports according to the ATC groups found 1 or more medicines in 83,427 reports. Thus, only 7.7% of the reports were excluded from the analysis. ATC groups A (Alimentary tract and metabolism), B (Blood and blood forming organs), C (Cardiovascular system), J (Anti-infectives for systemic use), and N (Nervous system) were consistently most frequently involved in the reported events covering altogether 80% (n=66,944) of the overall number of reports (Figure 12A). Furthermore, the N (Nervous system) class medicines were significantly more frequent in the reports affecting 27% of all reports. In a more detailed analysis, it was discovered that ATC subclasses N02 (analgesics) and N05 (Psycholeptics) covered 66% of all reports including N class medicines (Figure 12B).

Data from the annual medication consumption in public health care units (received from Fimea) indicated that the consumption was the highest for the ATC groups A, B, and C accounting for 64% of the total annual medicine consumption throughout the study period. Furthermore, the consumption of N subclasses N02 (Analgesics), N05 (Psycholeptics), and N06 (Psychoanaleptics) was significantly higher than in the rest of the subgroups. Thus, there was a clear association between consumption and the high number of medication-safety incident reports in ATC groups A, C, and N, as well as within N class in subgroups N02 and N05. Furthermore, ATC groups B and J were involved in a relatively high number of reports when annual consumption is considered (approx. 20% and 10% of annual
reports vs. 10% and 5% annual consumption, respectively). In contrast, the subgroup N06 had a relatively low number of reports with regards to the annual consumption (approx. 10% of annual reports vs. 20% annual consumption).

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5% annual consumption, respectively). In contrast, the subgroup N06 had a relatively low number of reports with regards to the annual consumption (approx. 10% of annual reports vs. 20% annual consumption).

The event types in the reports were recategorized into 6 groups (Figure 13). Throughout the 10-year data collection period, administration errors (29.4%) were the most common events reported, followed by dispensing errors (23.0%) and documenting errors (22.6%). Administration errors were the most common MEs reported whereas dispensing errors accounted for majority of the reported potential MEs (90.2% and 69.8%, respectively). The most common report subtypes in the case of MEs were administration of wrong medicine or the omission of medicine. Accordingly, the subtypes most commonly involved with potential MEs were medicines not being dispensed and missing documentation of medicines. There was no statistically significant difference in the distribution between event types and different ATC classes (p>0.05).

Fig. 13. Distribution of medication safety incident reports (Haipros) between event type categories. n = 83,427.

In majority of the reports, the reported incident was assessed to resulted in no harm (55.7%) or minor harm (20.1%) to the patient (Figure 14). Only 4.5% of the reports were assessed to cause either moderate or significant harm. Similarly, the reported events were most frequently assessed to inflict insignificant or minor risk (20.2% and 39.1%, respectively) with only 12.0%, 0.7%, and 0.1% of the reports assessed causing moderate, major, or serious risk, respectively. Statistically significant variation was detected between potential MEs and MEs in both risk and patient
outcome: in reports with ME, both risk and patient outcome were assessed more serious than in the reports describing potential MEs (p<0.001).

Fig. 14. The distribution of risk and patient outcome assessed in the medication safety incident reports by ATC codes.

In the second phase (III), medication safety incident reports from the year 2017 were extracted from the original data. Of the 5692 reports describing MEs, 1447 (25.4%) reports involving the TOP15 medicines from ATC groups A, B, C, J, and
N were included in the final analysis. Of the 1447 reports 168 (11.6%) included more than 1 medicine. The TOP15 medicines included in the analysis are presented in Table 7.

Table 7. The TOP15 medicines included in the second phase ME study (III).

<table>
<thead>
<tr>
<th>ATC class</th>
<th>Medicine class</th>
<th>Active substance</th>
<th>Medicine</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Insulin, fast-acting</td>
<td>Aspartinsulin</td>
<td>Novorapid®</td>
<td>76 (4.7%)</td>
</tr>
<tr>
<td>Insulin, slow-acting</td>
<td>Glargininsulin</td>
<td>Lantus®</td>
<td>57 (3.5%)</td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>Pantoprazole</td>
<td>Somac®</td>
<td>47 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Low MW heparin</td>
<td>Enoxaparin</td>
<td>Klexane®</td>
<td>380 (23.4%)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Warfarin</td>
<td>Marevan®</td>
<td>169 (10.4%)</td>
<td></td>
</tr>
<tr>
<td>Low MW heparin</td>
<td>Tinzaparin</td>
<td>Innohep®</td>
<td>91 (5.6%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Diuretic agent</td>
<td>Furosemide</td>
<td>Furesis®</td>
<td>147 (9.0%)</td>
</tr>
<tr>
<td>Adrenergic antagonist</td>
<td>Bisoprolol</td>
<td>Bisoprolol®</td>
<td>64 (3.9%)</td>
<td></td>
</tr>
<tr>
<td>Adrenergic agonist</td>
<td>Norepinephrin</td>
<td>Noradrenalin®</td>
<td>53 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>Intravenous antibiotic</td>
<td>Cefuroxime</td>
<td>Zinacef®</td>
<td>153 (9.4%)</td>
</tr>
<tr>
<td>Intravenous antibiotic</td>
<td>Cefuroxime</td>
<td>Cefuroxim®</td>
<td>62 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Peroral antibiotic</td>
<td>Cephalexine</td>
<td>Kefexin®</td>
<td>41 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Opioid</td>
<td>Oxycodone/Naloxone</td>
<td>Targiniq®</td>
<td>108 (6.6%)</td>
</tr>
<tr>
<td>Opioid</td>
<td>Oxycodone</td>
<td>Oxynorm®</td>
<td>95 (5.1%)</td>
<td></td>
</tr>
<tr>
<td>Pain and fever medicine</td>
<td>Paracetamol</td>
<td>Panadol®</td>
<td>83 (5.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MW = Molecular weight

Of the included reports, 1483 different MEs were identified using inductive content analysis methods. All MEs were divided into 5 ME outcome categories: excess medicine, omitted medicine, wrong dose, wrong medicines, and undefined outcomes. Omitted medicines was the most common outcome (33.9%, n=509) followed by undefined outcomes (19.4%, n=291), excess medicine (16.0%, n=240), wrong dose (15.8%, n=237), and wrong medicine (14.9, n=224). Of the wrong dose outcomes, 68.8% (n=163) were reports of too high dose and 32.2% (n=76) of too low dose. In the wrong medicine outcome, 79% (n=177) of the reports involved entirely wrong active substance and 21% (N=47) wrong formulation. The outcome of a ME was categorized as “undefined” if it was not clearly stated in the report. Such were, for example, the administration of medicine via wrong administration route, the administration of expired medicine, the administration of unsuitable medicine, and the administration of Warfarin (Marevan®) with no up-to-date prescription and dosage.
The error types involved in different ME outcomes are presented in Table 8. Overall, random error was the most common errors type resulting in different outcomes (26-35.3% depending on outcome group). Typically, random errors were simple mishaps in the medicine administration process, often referred to in the reports as “inadvertent error”. Together with errors in transferring or interpreting prescriptions and transferring information in the care interface, they were the cause of the majority of events. Most random errors resulted in the outcomes excess medicine, omitted medicine, and wrong dose involving the TOP15 medicines Klexane® (enoxaparin), Innohep® (Tinzaparin), Noradrenalin® (Norepinephrine), and Targiniq® (Oxycodone/naloxone). Furthermore, information transfer in the care interface and prescribing errors (35.2% and 13.7%, respectively) were the most common causes of “undefined outcomes” involving Somac® (Pantoprazole), Marevan® (Warfarin), and Noradrenalin® (Norepinephrine). More specifically, the most common errors with Marevan® and Noradrenalin® resulting in undefined outcome were the administration of Marevan® without up-to-date prescription and dosage and the administration of expired Noradrenalin®. The administration of the wrong medicine was typically caused by the administration of medicine to the wrong patient, LASA errors, and the administration of the incorrect insulin (51.8%, 16.5%, and 12.1%, respectively). The medicines most commonly affected by these errors were Novorapid® (fast-acting insulin), Oxynorm® (Oxycodone), and Cefuroxim® (Cefuroxime). Accordingly, Novorapid® was especially susceptible for being administered to the wrong patient whereas cefuroxime was typically confused with other intravenous antibiotics with a similar active substance name, e.g. ceftriaxone and ceftazidime. Furthermore, similar errors were not detected with the generic cefuroxime preparation (Zinacef®) also included in the TOP15 medicines indicating increased LASA risk specifically with Cefuroxim®.

There was no statistically significant difference in the distribution of the risk between the different outcome groups (p=0.71) (Figure 15). The majority (72.9%) of the MEs in all outcome groups was assessed causing insignificant or minor risk to the patient with an overall number of events with moderate risk of 373 (25.8%) and 19 (1.3%) with severe risk. The proportion of incidents with moderate risk varied from 22.6% (excess medicine) to 26.8% (wrong medicine). Similarly, the number of events with severe risk ranged from 0.4% (wrong dose) to 2.7% (wrong medicine). When the distribution of risk was assessed medicine-specifically, significant variation was detected between norepinephrine (Noradrenalin®) and other TOP15 medicines (p=0.04). Norepinephrine was the only TOP15 medicine with significantly increased susceptibility to high-risk events (OR 2.43, 95% CI
1.35-4.61). These events included e.g. the administration of expired norepinephrine, administration of the wrong medicine instead of epinephrine (LASA error), administration of the wrong dose, and the administration via wrong administration route.

Table 8. The most common MEs involved in different outcome categories (% within each category) and medicines with statistically significant susceptibility to different outcomes (OR, 95% CI, p<0.05).

<table>
<thead>
<tr>
<th>Excess medicine medicine</th>
<th>Omitted medicine</th>
<th>Wrong dose</th>
<th>Wrong medicine</th>
<th>Undefined outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Random error</strong> (26.0%)</td>
<td>Random error (35.3%)</td>
<td>Random error (33.3%)</td>
<td>Administering medicine to a wrong patient (51.8%)</td>
<td>Transferring information in care interface (35.2%)</td>
</tr>
<tr>
<td>Transferring information in care interface (23.1%)</td>
<td>Transcribing or interpreting prescription (20.6%)</td>
<td>Transcribing or interpreting prescription (25.3%)</td>
<td>LASA errors (16.5%)</td>
<td>Prescribing errors (13.7%)</td>
</tr>
<tr>
<td>Prescribing errors (4.1%)</td>
<td>Errors with printed lists (19.4%)</td>
<td>Information in care interface (7.6%)</td>
<td>Paper lists (5.2%)</td>
<td>Transferring information in care interface (5.4%)</td>
</tr>
<tr>
<td>Errors in documenting administration (3.7%)</td>
<td>Others (5.2%)</td>
<td>Calculating errors (3.6%)</td>
<td>Paper lists (2.7%)</td>
<td>Transferring in care interface (5.4%)</td>
</tr>
<tr>
<td>Technical errors in administration (1.2%)</td>
<td>Technical errors in administration (3.8%)</td>
<td>Technical errors in administration (3.6%)</td>
<td>Transactions (3.9%)</td>
<td>Using expired medicine/mishandling medicine (6.5%)</td>
</tr>
<tr>
<td><strong>LASA errors</strong> (1.2%)</td>
<td><strong>Others</strong> (1.2%)</td>
<td><strong>LASA errors</strong> (2.0%)</td>
<td>Technical errors in administration (3.6%)</td>
<td><strong>LASA errors</strong> (1.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medicine</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Klexane®</strong> (2.01, 1.47-2.75)</td>
<td><strong>Klexane®</strong> (1.89, 1.45-2.45)</td>
<td><strong>Noadrenalin®</strong> (2.64, 1.42-4.90)</td>
</tr>
<tr>
<td><strong>Innohep®</strong> (1.69, 0.97-2.94)</td>
<td><strong>Targiniq®</strong> (1.94, 1.17-3.20)</td>
<td><strong>Cefuroxime®</strong> (3.13, 1.73-5.65)</td>
</tr>
</tbody>
</table>
Fig. 15. The distribution of assessed risk between ME outcomes (A, B) and the TOP15 medicines (C, D).
5.3 Geriatric hospital admissions to tertiary care caused by adverse drug events (IV)

The 290 ED admissions included were made by 287 patients. All patient admissions were divided into three groups according to patient age for further analysis: 65-74 year, 75-84 years, and 85-95 years. The average patient was 77 years old, had 4.5 diagnosed comorbidities, and was using 7.5 medicines regularly with an additional 2 medicines taken when necessary. There were differences in the amount of medicines used between the age groups: on average, the number of regularly used medicines in the oldest and the youngest groups was 8.9 and 6.6, respectively ($p=0.012$). Similarly, the oldest age group had an average of 3.1 medicines taken when necessary compared to the 2.0 in the two younger age groups. Similarly, the average number of comorbidities was also found to increase with age from 3.5 in the youngest age group to 4.8 in the oldest ($p=0.004$). The majority of patients (90.7%, $n=263$) were community dwelling. Residency did not increase the risk for polypharmacy ($p=0.268$). Of the patients, 157 were treated in the specialty of internal medicine, 68 were surgical patients, 59 neurological patients, and 6 from other specialties.

Of the studied admissions, 67 were found probably of possibly medication-related (38 and 29 admission, respectively). Polypharmacy (OR 3.3, 95%CI 1.5-6.9, $p=0.01$) was the only patient characteristic that was found to increase the risk of hospitalization: age, sex, residence, or specialty did not affect the outcome (minimum $p=0.077$) (Table 9). However, patients from the specialty of internal medicine were overexpressed in the sample whereas patients from the surgical specialty were under-expressed. This was caused by exclusion of surgical patients due to missing medication information in the sample. Although sensitivity testing indicated that this did not distort the remaining take, it was a clear indication of field specific problems in medication reconciliation during at the time of admission.

Table 9. Comparison of medication-related admissions versus non-related admissions (n=290).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ADE (n=67)</th>
<th>No ADE (n=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [y: mean ± SD (range)]</td>
<td>79.2 ± 7.9 (65-95)</td>
<td>76.3 ± 7.3 (65-95)</td>
</tr>
<tr>
<td>Comorbidities [mean ± SD (range)]</td>
<td>4.9 ± 2.5 (0-16)</td>
<td>3.9 ± 2.6 (0-18)</td>
</tr>
<tr>
<td>Number of regular medicines [mean ± SD (range)]</td>
<td>9.1 ± 4.0 (0-22)</td>
<td>6.8 ± 4.5 (0-22)</td>
</tr>
<tr>
<td>Number of medicines used when necessary[mean ± SD (range)]</td>
<td>2.8 ± 2.2 (0-11)</td>
<td>2.0 ± 2.3 (0-15)</td>
</tr>
</tbody>
</table>
The adverse events leading to hospitalization, and the medicines involved in the events are presented in Figure 16. The assessment in this study only considered whether the admission was medication-related but not whether the event was preventable or not. Falling, vertigo and fractures were slightly more frequent than the rest of the events. ATC class N (Nervous system) medicines were significantly more often involved in the events than medicines from other ATC classes. Overall, they covered over half (52.9%) of all drugs involved in the events. Furthermore, opioids (N02A), antipsychotics (N05A), and antidepressants (N06A) were the N class medicines which appeared most frequently in the events, covering nearly two thirds (59.4%) of all the N class medicine events. Only 40.3% of ADEs resulting in hospitalization were detected at the time of admission.

When compared with each other, causality assessment conducted using the customized Naranjo scale or by the research team resulted in near-equal number of cases with doubtful correlation between medication and hospital admission (226 and 223, respectively). The total amount of probable and possible cases was also similar with both methods. However, the assessment using the customized Naranjo scale resulted in a higher amount of possible cases whereas the assessment by the research team had a higher number of probable cases.
Fig. 16. Events causing geriatric hospitalization (C) and medicines involved in them (A, B).
6 Discussion

This study described and analyzed medication-related adverse events in specialized health care. It captured factors related to special patient groups, high-risk medicines and processes by employing both large, nationwide databases as well as local real-world data from the university hospital EHRs. Consequently, it provided the first nationwide description and overview of the current situation of medication-related adverse events in the Finnish tertiary care units.

6.1 Medication-related adverse events in tertiary care

This research project has shown that hospital-acquired medication-related adverse events are highly common in the Western World (I). In the first phase, a pooled estimate of inpatient ADEs indicated that close to one fifth (19%) of all inpatients are affected by various drug-related adverse events during admission (I). Despite the high heterogeneity detected in the prevalence of ADEs, the results are supported by numerous studies showing similar estimates of ADE frequencies (Hakkarainen et al., 2012; Miguel et al., 2012; Panagioti et al., 2019). As previous research combined with the results from this research project support the high overall rate of medication-related adverse events, they can be considered one of the most alarming safety concerns of current medicine. This is also further emphasized by the approximations of nearly 200 000 annual deaths caused by medicines in Europe alone (European Commission, 2008). Moreover, these figures still represent a mere fraction of the total effect medication-related harm has in health care as the majority of medication-related events are never detected due to considerable under-reporting (Classen et al., 2011; Tchijevitch et al., 2017). Often the less serious reactions, regardless of the severe morbidity and lowered quality of life caused, remain unacknowledged. As a result, the true extent and consequences of medication-related harm are far greater, and the number of patients affected by them significantly higher than those presented in the statistics.

The most frequent inpatient events in this study were CNS events, renal dysfunction/electrolyte disturbances, allergic reactions, and hematological events or bleeding (I). When fatal events occurred, they were most likely due to hematological events (bleeding) or renal dysfunction/electrolyte disturbances. Furthermore, in the analysis of geriatric hospital admissions, falling, vertigo, and fractures were the most common causes of hospitalization in this patient group (IV).
Similar results have been presented in previous studies concerning both inpatient and outpatient ADEs and ADRs thus further highlighting the universal nature of medication-related harm: Regardless of country, health care setting, and patient population, similar problems arise in pharmacotherapy (Alhawassi et al., 2014).

With the acknowledgement of medication-related harm causing both functional and economical challenges to health care systems globally, the underlying reasons have been under intensive scrutiny. Along with similarities in medical practices and guidelines, one of the most important factors linking all western countries in this matter is the increase in the average age of patients (Alhawassi et al., 2014; Asaad Assiri et al., 2018; Hoonhout et al., 2010; Krähenbühl-Melcher et al., 2007). All developed countries, Finland included, have been facing a rapid change in the age structure of the society during the past decades (Official Statistics of Finland (OFS): Population projection (e-publication), 2018). The overall number of geriatric patients has quickly increased causing major strain for health care systems. Consequently, the aged are also a high-risk group for medication-related harm (I, Alhawassi et al., 2014; Krähenbühl-Melcher et al., 2007).

In addition to being susceptible to hospital-acquired ADEs, geriatric patients have a significantly increased risk for outpatient ADEs resulting in hospitalizations (Alhawassi et al., 2014; Beijer & de Blaey, 2002). In this study it was found that in 2014 nearly a quarter (23.1%) of geriatric EC admissions to a Finnish university hospital were drug-related (IV). As events requiring hospitalization represent the most serious types of events, the tip of an iceberg, this raises concern for the overall situation of pharmacotherapy in the elderly. In this study it was also discovered that less than half of the ADEs requiring hospital care were identified during admission, thus again highlighting the fact that the phenomenon is not only common but also poorly identified with current practices (IV). The results also suggested that patients treated in the surgical specialty were more likely to not have their medication regimen checked and documented during admission due to inadequate medication reconciliation. As these patients were equally likely to suffer from medication-related harm, this would predispose them to both delayed diagnosis and treatment. Although it was not specified whether the harm causing hospitalization was preventable or not, the results showcase both the gravity of the effect medication-related harm can have in this patient group as well as the added burden that unplanned hospitalizations, worsened by poor practices, can have on health care. As the proportion of aged people society will keep increasing in the future, the problem with medication-related harm can be expected to exacerbate unless
effective measures are taken in both event prevention and improving current medication practices.

This research project also established that the majority of medicines involved in medication-related adverse events are from 5 different ATC groups: A (Alimentary tract and metabolism), B (Blood and blood forming organs), C (Cardiovascular system), J (Anti-infectives for systemic use), and N (Nervous system). The most common ATC groups involved in hospital-acquired ADEs, ADRs, and FADRs were N (nervous system), C (Cardiovascular system), J (Anti-infectives for systemic use), and B (Blood and blood forming organs) (I). Furthermore, the same medicines, along with preparations from the ATC group A (Alimentary tract and metabolism), consistently appeared as the medicines most commonly involved in in-hospital ME reports throughout the 10-year data collection period (II, III). Consequently, these results were supported by previous research by Graciano Silva et al. (2018). They also endorse the current understanding where MEs are considered major contributors to adverse events resulting from drugs. The importance of understanding the association is emphasized by the estimate that roughly 30-50% of all ADEs are preventable, i.e. resulting from MEs. As N (Nervous system) medicines was also the medicine group most commonly involved in outpatient ADEs resulting in geriatric hospitalizations, focus on the medication processes involving medicines from these groups needs addressing.

It is possible, that the tendency of these medicines to occur in association with medicine-related harm is partly a consequence of their extensive use in the majority of the common conditions treated today: all groups appear frequently in medication regimens for patients with e.g. diabetes, coronary diseases, infections, and several psychiatric conditions. With current medical practices, patients are better diagnosed and treated than ever before. This has also had a significant impact on the consumption of these medicines and, for years we have been witnessing an increase in their annual consumption rates (Finnish Medicines Agency Fimea, 2017). On the other hand, measures to ensure the safe use of medicines have not been expanding at the same rate. As a result, we have reached a situation where medicines with the potential for causing harm are more often used than ever before but the processes for ensuring long-term safety and actions to minimize adverse events lag behind this development.

The significant increase in the use of medicines has resulted in growing numbers of patients affected by polypharmacy, i.e. the use of 5 or more concomitant
medicines. Moreover, polypharmacy has also been established as a risk factor with the strongest correlation to medication-related adverse events (I, IV, Alhawassi et al., 2014; Asaad Assiri et al., 2018; Härkänen et al., 2018). Understandably, a complex medication regimen can cause problems both in the inpatient and outpatient setting due to mix-ups and confusion. Furthermore, incorporating various active substances significantly increases the risk of pharmacological and pharmacokinetic interactions e.g. by disturbing drug metabolism or by causing heightened additive effects. It has been estimated, that in elderly patients the addition of 1 medicine to the medication regimen will cause an increase of 10% in the probability of ADR, and rise of up to 75% if more than 5 medicines are used (Byles, Heinzé, Nair, & Parkinson, 2003). Although other factors, such as length of hospital stay, multimorbidity, female gender, and Caucasian race, have also been linked to higher susceptibility for medication-related harm, polypharmacy remains the only risk factor with a clear correlation for an increase in both in-hospital events as well as outpatient events resulting in hospitalization (I).

Despite being linked to an increase in medication-related harm, the use of medicines, polypharmacy even, has provided a means for curing, treating, and improving the quality of life in many conditions that were previously deemed untreatable. This has partly been achieved by effectively combining multiple medicines with an additive effect to treat certain conditions. Thus, the issue of unwanted effects should not be managed by simply restricting prescribing and avoiding the use of medicines altogether but by endorsing rational guidelines on medication practices. For reinforcing this, up-to-date information should constantly be collected, analyzed, and revised in order to ensure medications with appropriate risk-benefit profiles are used in the general population. Consequently, research, sufficient education, and efficient monitoring form the basis for creating national recommendations for rational use of medicines. These functions are also highlighted as national goals in the program for rational use of medicines by MSAH (Ministry of Social Affairs and Health, 2018a).

### 6.2 Surveillance with voluntary reporting

A significant part of the data used in this research project consisted of the national medication safety incident (Haipro) data which was granted for use in this project by the FSPS. The Haipro data, which has now been collected for over 12 years, forms the largest database on medication safety incident reports in Finland with an average of 15 000 reports annually made in tertiary care units (Rauhala et al., 2018).
It is a conventional incident reporting system, thus displaying all the typical advantages and disadvantages of such a system: regardless of the evident underreporting and overexpression of certain types of reports, it produces a low-cost method for promoting opportunities for organizational learning (Howell et al., 2016; Manias, 2013; Montesi & Lechi, 2009). Furthermore, in Finland it is currently the only method available for gaining awareness about concurrently occurring errors in the medication process. However, as all such systems, the Haipro system is not able to describe but a small fraction of all events that occur in an in-hospital setting.

As already stated in the publication by IOM in 2000, the chance of error lies in all processes executed by people, as “to err is human” (Kohn, Corrigan, & Donaldson, 2000). Thus, for a long time, there has been a growing understanding of the importance of identifying stages susceptible to errors in the medication process. The results from the Haipro data used in this research project provided information about both high-risk medicines as well as processes prone to errors in the in-hospital setting. As it turned out, even with the 1-year-sample used in this study, it was possible to identify several specific errors occurring frequently in the health care units, e.g. the increased susceptibility of Cefuroxim® to LASA errors, increased susceptibility for administering fast-acting insulin to a wrong patient, recurring issues with inappropriate administration of low-molecular weight heparins, problems with up-to-date prescriptions concerning warfarin, and the tendency of administering expired norepinephrine (III). By simple screening methods it was also possible to extract the medicines most commonly involved in the events on a nationwide level (II, III). Furthermore, the in-depth analysis of 1447 medication safety incident reports indicated a contradiction between the risk assessment conducted within the organizations and that expected from the analysis of event outcome and medicines involved (III). For example, it was determined that the most common event involving fast-acting insulin was administering it to the wrong patient – a mistake known for its fatal outcomes in the past (Classen, Jaser, & Budnitz, 2010; Geller et al., 2014). However, only the events concerning the administration of norepinephrine were consistently assessed high-risk in the reports, indicating severe limitations in the current assessment process of reported events.

These results demonstrate one of the most important outcomes of this research project: the enormous value and potential of the Haipro data collected from the Finnish health care organizations. As it was proven, it can reach and collect information otherwise unattainable through additional methods currently in use. Furthermore, although currently mostly used organization specifically, it also holds
the potential for continuous nationwide analyses of the underlying problems within health care. However, as analyses comparable to that in this research project have not been consistently performed before, it is evident that the data is currently poorly utilized: despite its vast potential in providing information for patient safety improvements, only a small fraction of this potential is efficiently used with current practices. The present situation not only undermines the benefits gained from the data but also diminishes the overall value of the reports. Moreover, it reduces the general credibility of such a reporting system.

One of the key reasons for the poor utilization of the Haipro data lies in the format in which it is produced. Although some parts of the reports are provided in categorical form, the most informative parts, i.e. medicines involved and the description of the event, are in narrative form. Consequently, the analysis of such data requires specialized tools and methods which, to date, have been lacking. In addition to the challenges with data processing, the comprehensive utilization of the Haipro data is debilitated by the single volume of reports collected from the organizations: although the large number of reports is considered a positive problem and health care personnel are further encouraged to increase the amount of reporting, the sheer mass of the data poses growing challenges for the methods used in the analysis. Accordingly, current methods have only been able to produce a narrow description of the incidents occurring within health care units, thus emphasizing the need for advanced methods for the comprehensive utilization of Haipro data in the future.

To answer this demand, accompanying incident reporting with computerized analysis methods and data mining has gained international popularity (Gandhi et al., 2000; Thürmann, 2001). Through the incorporation of these methods, data extraction from the narrative part of the reports can be automated, thus enabling fast and effective means for quick analyses of large quantities of diverse data. Consequently, it provides opportunities for conducting more complex analyses early on in report processing, making it easier to abstract data and form conclusions of a set of reports from e.g. certain time period or specialty (Montesi & Lechi, 2009). More importantly, however, it allows the organizations to progress from learning to evidence-based action as the awareness of current problems arising from medicines, devices, or processes are received consistently and more rapidly from the reporting system. Instead of collecting data for retrospective analysis, health care organizations can concentrate on improving practices based on error signals received from different units with a significantly shorter lag time. If the automated methods are further developed with machine learning, such systems could also pose
predictive value by forecasting potential error situations or medicines more prone
to certain error types. Thus, it would also change the nature of organizational
learning from improvements derived out of hindsight to creating approaches for the
prevention of likely errors. Furthermore, if similar analysis was conducted in all
organizations nationwide, the system could assist in performing national
recommendations and medication safety bulletins as a part of active patient safety
work on a larger scale, simultaneously promoting the utilization of health care data
as recommended in the Rational Pharmacotherapy Action Plan by MSAH (Ministry
of Social Affairs and Health, 2018a).

Along with improved processing and analysis of the reports, the heterogeneity
detected in the variables assessed within the reports requires addressing. Currently,
several features of the reports, e.g. risk caused by the events, patient outcome, and
event type, are assessed by the person handling the reports within the organization,
typically the superior within each unit. As demonstrated before, the assessments
conducted by several different people have resulted in high heterogeneity in the
assessment results (I, Holmström et al., 2018). Certain variables, such as the risk
and outcome related to the events, have significant importance in determining the
final course of procedures the report results in, the assessment process has
significant importance in the overall impact of the report: as with current practices,
information of events assessed to be minor or insignificant in risk are dealt with
within the units whereas only the more serious events reach higher levels in the
organizations. Besides heterogeneity, this practice creates a setting where the
overall state of medication safety is thoroughly managed by no one.

To resolve the issue of inconcise assessments and the division of medication
safety management, the processing, assessment, and analysis of medication safety
incident reports should be focused within each organization. The management of
all medication safety information through one body would probably significantly
improve the quality of information gathered from the results but could also
facilitate the unification of medication practices and thus reinforce evidence-based
actions throughout the organization. Furthermore, such procedures would better
enable the use of pharmacological expertise in assessment and decision-making,
both of which are actions encouraged by MSAH in planning future health care
structures (Ministry of Social Affairs and Health, 2018a).

In the future, the estimates of the development of event prevalence pose
increased pressure for improvements concerning safety in medical care. Regardless
of its potential, the Haipro data and current methods alone will not suffice to answer
this demand: as demonstrated by previous research, different detection methods tend to favor the identification of certain types of events causing bias in the analysis (Gandhi et al., 2000; Montesi & Lechi, 2009). Consequently, using just one method in the overall management of medication safety would result in poor coverage of the total spectrum of medication-related adverse events. To answer the future demand in event detection and prevention, the utilization of more than one method in the health care organizations is needed. Furthermore, as none of the methods currently available have proven effective in reaching incidents in all care stages and settings, comprehensive covering of events requires the combination of all methods available. Although patient safety has an intrinsic value in health care, such an undertaking would require major contributions from several aspects, inevitably also raising the question of economics. However, with current estimates of costs related to ADEs, ADRs, and MEs it could be discussed whether not investing in the development in this area is something the Finnish health care system can afford in the future.

6.3 Safety culture in health care

The past 20 years have marked the beginning of patient safety work in many countries. As the prevalence of medication-related adverse events and the harm resulting from them has gained attention, it has initiated the development of safety actions beginning from improved safety profiling during product development phase, further extending to enhanced monitoring of ADE signals throughout the drugs life-cycle. Moreover, patient safety work now covers levels from individual health care organizations to national and international assemblies in the field. This has yielded guidelines, action plans, and surveillance systems that are now used worldwide for improving the safety and quality of medical care. Accordingly, similar development has also been actively ongoing in Finland and has resulted in the launch of several laws, Acts, and functional approaches - the Haipro system being one of the most prominent examples of this. However, growing evidence shows that in the success and sustainability of the improvements made by novel methods and practices towards clinical quality and care safety, a change in the larger organizational culture is needed (Burnett et al., 2010; Nieva & Sorra, 2003).

This realization has provoked the concept of safety culture in health care organizations. The simplest way to define this is the consideration of an organization wide commitment in all actions, processes, and practices towards high-quality, safe health care. Since then, safety culture has become an important
concept in health care, emphasizing the motivation and determination to improve patient safety. Instead of keeping safety considerations within selected groups in the administrative level, it has extended the right but also the responsibility of this work to reach all units and members of the organization. As the attitudes of health care professionals towards safety have been shown to significantly impact the prevalence of ADEs and MEs, this approach is hoped to enhance the impact of reducing these events (Bonner, Castle, Men, & Handler, 2009). Although it may appear to be highly theoretical, the importance of a positive safety culture within the health care organizations has been demonstrated in studies showing significant improvement in patient outcomes with decreased mortality, decreased length of stay, decreased MEs, and increased patient satisfactions (Huang et al., 2010; Sorra, Khanna, Dyer, Mardon, & Famolaro, 2012). Thus, safety culture comprises of not only the concrete actions taken towards diminishing medication-related harm but also of the shared beliefs, attitudes, values, and norms of health care professionals.

While surveillance systems, such as the Haipro system, have brought safety work closer to health care professionals with opportunities for better involvement by reporting events, it has also brought up issues to consider in the process. Incident reporting, although forming the very basis of safety culture and organizational learning, can also foster culture of blame: instead of emphasizing the possibility for positive change, employees can experience shame inflicted by the reports. Furthermore, with current pressure caused by growing patient flows, the idea of productivity over safety within units can have a negative effect on both patient outcome and employee safety by increasing the likelihood of accidents and employee injuries (Mohr, Eaton, McPhaul, & Hodgson, 2018). Thus, safety culture is not only sustaining safe care for patients but addressing occupational health and safety of employees, making it important for the overall functioning of health care systems.

An example of the impact of attitudes towards recommendations and safety concerns of medicines can be taken from the 1990s with the case of Cisapride (Smalley et al., 2000). Cisapride was used for nocturnal heartburn and known to be metabolized by the CYP3A4 enzyme in the liver. Shortly after being granted marketing permission in the US, several reports were received of Cisapride causing serious and even fatal cardiac arrhythmias when used by patients concomitantly using CYP3A4 inhibitors or with cardiovascular comorbidities. As a response to this, a black box warning was added to Cisapride’s packaging while the drug manufacturer informed all health care professionals of these contraindications with
a letter. When the FDA evaluated the effects of these interventions, it was discovered that the inappropriate use of Cisapride had decreased by mere 2%. As the serious adverse events did not decrease, Cisapride was finally withdrawn from the US market in 2000. Regarding the current knowledge of safety culture, this leaves us wondering whether Cisapride was unsuitable for medicinal use to begin with or whether a safe drug was made fatal by disregard of pre-existing knowledge of safe use.

Regardless of the correct answer to the question of the case of Cisapride, the take home message of the example is clear: accounting for the safety of each patient treated within health care cannot afford creating harm with our own conducts. Pharmacotherapy, as described by its symbol, the double-bladed sword, will always be a balancing act between harm and benefit. With disregard of safety concerns and inappropriate use of medicine, we can make the safest drug fatal. Nonetheless, with effective research, evidence-based practices and the development of patient safety in all levels of care, we have the possibility to ensure the safety and effectiveness of health care in the future.
7 Summary and conclusions

Medication-related adverse events (ADEs, ADRs, and MEs) are highly common in the inpatient setting. In this research project it was shown that they affect up to one fifth (19%) of hospitalized patients and can cause close to a quarter (23.1%) of geriatric hospitalizations (I, IV). The most common ADEs identified in hospitalized patients were CNS events, hematological disorders, and renal dysfunction or electrolyte disturbances (I). The most typical ADEs leading to geriatric hospitalization are falling, vertigo, and fractures (IV). Approximately one third of ADEs and ADRs are preventable (I).

The majority of MEs occurring in tertiary care are administration errors, documenting errors, or dispensing errors (II). Approximately 42% of the reported events were potential MEs and 58% MEs, i.e. events that reached the patient. Most reported events included medicines from ATC groups A (Alimentary tract and metabolism), B (Blood and blood forming organs), C (Cardiovascular system), J (Anti-infectives for systemic use), and N (Nervous system) (II). Accordingly, the same ATC groups were most commonly found to be involved in both geriatric hospital admissions as well as in inpatient ADEs and ADRs, highlighting the important association between MEs, ADEs, and ADRs.

Of the 5 most common ATC groups, N (Nervous system) class medicines had the highest frequency in inpatient MEs, geriatric hospitalizations, and inpatient ADEs (I, II, IV). In more detailed analysis, opioids and antipsychotic medicines were identified as the ATC subgroups that were most commonly involved in these events. This trend can partly be explained by the high annual consumption of these medicines in the health care units. On the other hand, medicines in these groups are known for their high-risk potential for adverse events when used in the elderly. According to the inpatient MEs, the events involving the N class medicines were not assessed as more serious than the events involving other ATC groups medicines (II).

The results of the in-depth analysis of tertiary care TOP15 ME reports from 2017 identified “omitted medicine” as the most common ME outcome (III). Although many of the analyzed MEs described events with potentially severe consequences to the patient, only the events including norepinephrine were significantly more commonly assessed as serious within the organizations thus revealing problems in the current assessment process. In this research project, factors increasing the risk for medication errors and adverse drug events were
higher age, increased length of stay, multimorbidity (I), and polypharmacy (IV). Of these factors, higher age was the only factor associated with the prevalence of medication-related adverse events in both the inpatient and outpatient setting (I, IV).

The increasingly complex medications together with an aging population cause pressure in providing safe medical care. As such, medication-related harm causes major increase in both patient morbidity and economic consequences. Consequently, rapid developments are required in order to manage this with the increasing need for resources available for health care. Event surveillance and the development of medication processes creates the basis for better knowledge on medication-related safety concerns, forming the basis for organization learning and improved patient safety in the future (Figure 17). Thus, further research is needed in the development and implementation of novel and more efficient methods for both surveillance and prevention of medication-related adverse events.

**Fig. 17. Prospective for the process of developing safer pharmacotherapy through organizational learning in the future.**
References


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Original articles


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