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Morbidity and mortality of multimorbid patients are raised by increased drug-drug and drug-disease interactions.

MASTERARBEIT

zur Erlangung des akademischen Grades

Master of Medicine (M Med) der Medizinischen Fakultät der Universität Zürich

vorgelegt von

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1. Abstract

Purpose: Multimorbid patients often take many different medicaments at the same time. Those can have clinically relevant interactions or can be overdosed, due to neglected interactions or organ insufficiency. Especially in patients with renal insufficiency this can happen very easily. The aim of this study is to investigate whether multimorbid patients suffer from more medication errors than non-multimorbid patients.

Methods: Anonymous patient data of 2014 from the University Hospital of Zurich were used to perform a retrospective data analysis. There are different kinds of medication interactions. First, there are drug-drug-interactions, which happen when two contraindicated medicaments are falsely given together and can lead to an adverse drug reaction. Other interactions covered in this study are drug-disease interactions and dose adjustment errors, where a drug has not been dose adjusted correctly in a patient with renal impairment. These interactions were identified for in the data and along their effects on patients' mortality and morbidity.

Results: We could show that the more diagnoses a patient has, the more likely it is that the patient has a medication error. The mortality of patients who had medication errors was 5.1% whereas the mortality of patients without medication error was at 2.3% ($p<10^{-12}$). It was also shown that patients with medication errors stayed longer in the hospital (15.6 days) versus the patients without medication errors (6.5 days) ($p<10^{-15}$).

Conclusions: Medication errors are a big problem in today's hospitals. Due to increased life expectancy multimorbidity is increasing and thus also medication lists are getting longer. In the environment of a hospital drugs are often falsely prescribed in a contraindicated combination or not dose adjusted for renal impairment. Those have a clinically relevant impact on the patient who is more likely to have an exaggerated course of disease leading to a higher mortality. The average length of hospital stay is also getting longer which implies that the medication interactions have an impact on patients' morbidity and thus success of treatment.

2. List of abbreviations

NSAID: Nonsteroidal anti-inflammatory drugs

SSRI: Selective serotonin reuptake inhibitors

ADR: Adverse Drug Reaction

ACE-Inhibitors: Angiotensin-converting enzyme inhibitor

ASS: Acetylsalicylic acid

eGFR: estimated glomerular filtration rate

NCS B-agents: Non-cardio selective beta agents

3. Introduction

Today's medicine enables people to get older than ever before. Before untreatable diseases are now cured with a huge variety of interventions and medications – life expectancy increases yearly (1). Advanced age and the associated illnesses cause that elderly people have to take a large number of medications to treat those or keep them from progressing further (2). When taking different medications combined there is always a risk of having a side effect, an adverse drug reaction (ADR). ADR are injuries caused by taking a single drug or as a result of a combination of two or more drugs. They can manifest in a wide range of symptoms, ranging from a skin rash or a headache to severe symptoms such as intracranial bleeding. ADR have the potential to increase mortality and morbidity. (3) (4)

Often there are contraindicated combinations of drugs. As the medication lists of multimorbid patients are getting longer, it is more likely that such maliciously interacting drugs are falsely given together (5). Another cause of adverse drug reactions are medications that should not be prescribed when a patient has a certain disease, for example non selective beta blockers and asthma (6). Such interactions were also examined in this study.

Another important issue in adverse drug reactions is overdosing. Drug dosages are normally standardized for every medicament but sometimes have to be adjusted for patients with renal impairment. This can be overlooked easily and can lead to a higher concentration of the active component in the body of the patient because the kidney can not excrete these substances at a normal rate, leading to an accumulation of the substance, which then causes overdosing toxicity. (7)

This study analyzes the effect of medication errors on the mortality and morbidity of the patients using the patient data of 2014 of the University Hospital of Zurich. Commonly falsely prescribed combinations of medication were searched for in the medication lists of the patients; therefore we retrospectively analyzed the effects of these interactions on the health of the patients. Using parameters such as the average length of hospital stay, it can be concluded what effect the medication errors have on the course of the disease and patient's health.

4. Methods

4.1. Study design

The University Hospital Zurich yearly treats about 500'000 Patients in an out-patient setting and more than 38'000 patients as in-patients. The large number of patients with different diseases and treatments proves to be an optimal basis for a retrospective data analysis. This study is based on the patient data of 2014, in which every in-patient is registered in an anonymized database. This leads to a dataset including 38'793 patients and containing information about the patients age, sex, insurance and other demographic data, but also the diagnoses encoded by ICD-10. It also includes patients medication lists formalized as ATC codes. Furthermore all of the laboratory data that were acquired for a patient over the course of his hospital stay are also included into the database.

4.2. Data collection and variables studied

To identify drug-drug interactions, drug-disease interactions and failed dose adjustments, we first defined a reference list on what to search for in the data. It was looked for known medication interactions that are often prescribed together and are contraindicated. Often prescribed medicaments such as NSAID are used to treat a variety of symptoms like pain, fever and inflammatory signs and can be falsely given to the patient without checking the patients' medical history. A major concern was to find often prescribed medications, as they are more likely to be combined with a contraindicated drug and also to find medications that are heavily contraindicated in combination because they could have severe effects on the patients' health. As it was not the goal of the study to find all possible medication errors, table 1 shows the list of chosen interactions that are divided in the different interaction classifications. To get a good overview of the whole spectrum of adverse drug reactions, a variety of different medications were chosen to get an overview in the different specialties in today's medicine.

Drug-disease interactions	Drug-drug interactions	Dose adjustment
- Digoxin + potassium <2.8mM - potassium sparing diuretics + potassium >6mM - non cardio selective beta blockers + asthma - Metformin + eGFR <30 - Metoclopramide + Parkinson's - Thiazides (ex. Metolazone) + eGFR <30 - NSAID + eGFR <30	- Phenprocoumon + NSAID - Verapamil + Propanolol - loop diuretics + NSAID - NSAID + SSRI - SSRI + Triptane - ASS + Ibuprofen - ACE-Inhibitors + NSAID - Amiodarone + Haloperidol	- Levetiracetam - Pregabalin - Rivaroxaban

Table 1 Drug Interactions

Morbidity and mortality are influenced by different factors including the patient's actual health, his co-morbidities and the number of substances he has to take. To be able to show that the medication interactions have a significant effect on the patients outcome, patients health had to be quantified to make sure that it's not just the higher number of diagnoses and substances that lead to an increase in mortality and morbidity. A coefficient was formed consisting of the duration of stay divided by the predicted duration of stay by DRG, which defines an optimal duration of stay with a certain disease. This helped to answer the question if the medication interactions had an effect on the duration of stay. A coefficient of 1 means that the patient's hospital stay was as long as predicted, where as a coefficient of >1, it similes a longer stay than predicted and it could be assumed that the interactions had an effect on the patients outcome.

4.3. Statistical analysis

For the analysis of the patient data a python script (www.python.org) was used. It allowed analyzing the vast amount of data for medication errors. Queries were programmed that searched in every patients medication list, whether drugs that are contraindicated were given within 24 hours using table 1 as reference. Also for laboratory data

such as eGFR or potassium there always had to be a maximal gap of 24 hours between the test result and the application of the next medicament to ensure that the patient was given the medicament when a contraindicating laboratory value was present in that moment.

This resulted in a database quantifying the drug interactions for every patient. With this information, it was possible to identify how many interactions a patient had on average, how many diagnoses those patients with a high number of interactions had and how many different substances were taken in total.

This table was imported and analyzed with R (www.r-project.org) and graphics such as boxplots and histograms to visually present the result were generated with this programm.

5. Results

5.1. Patient characteristics

Based on the patient data of the University Hospital Zurich of the year 2014, 38’793 patients were analyzed for medication interactions listed in table 1. The examined patients consisted of 18’977 men (49%) and 19’816 women (51%) in which the mean age was 49 $\pm$ 24 years (range: 1-104 years). On average every patient took 5.9 $\pm$ 4.9 substances (range: 1-51). The average length of hospital stay was 6.8 $\pm$ 9.7 days (range: 1-299 days). The total number of individual doses of medication taken by a patient was on average 92.4 $\pm$ 201.3 (range: 1-6334). Of the 38'793 treated patients, 924 died (2.3%) in the course of their hospital stay.

5.2. Outcome

Patients with a high number of diseases had more medication errors than patients who had less than 10 diagnoses. As figure 1 shows, there is a correlation between the number of diagnoses and the number of drug interactions.

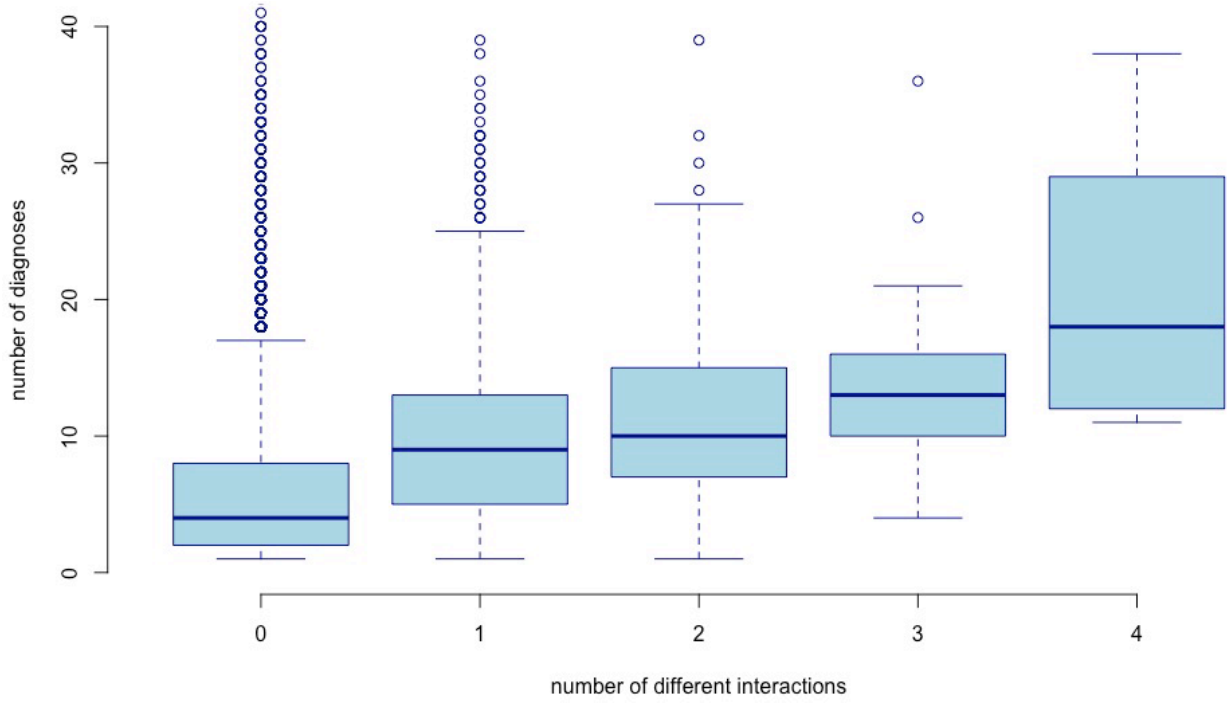

Fig. 1 Patients with a high number of diagnoses are more likely to have medication errors. Boxplot showing the number of diagnoses relative tot he number of different interactions. Bar in the middle = median, box = 25-75% Perzentile, Whiskers = 5-95% percentile.

Patients who had to take more medications had more medication errors than persons that only took a small amount of different medications, a correlation that is trivial and expected. Figure 2 shows the number of medications a patient received in the course of his hospital stay and the corresponding medication interaction.

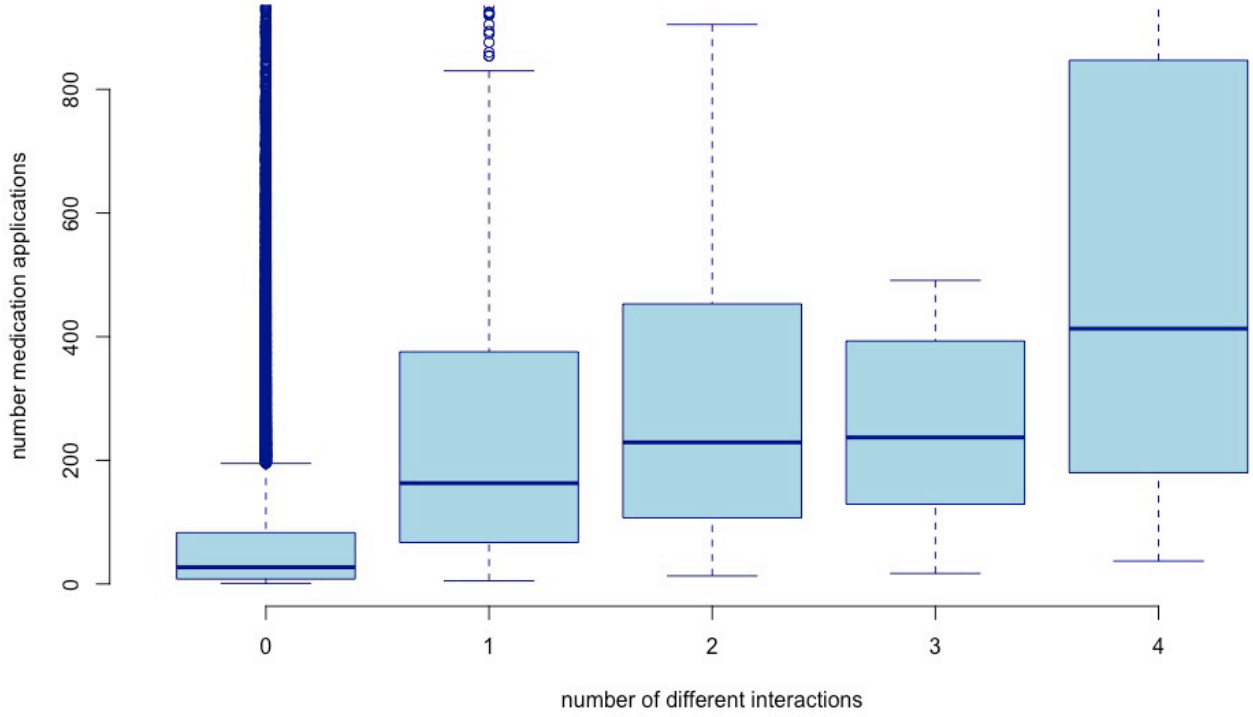

Fig. 2 Patients which have to take many substances over their course of hospital stay are more likely to have medication errors than patients with a lower drug-count. Boxplot showing the number of drug applications relative to the number of different interactions. Bar in the middle = median, box = 25-75% percentile, Whiskers = 5-95% percentile.

The mortality of patients without medication error was 2.3%. Those patients that had a minimum of one medication error had an average mortality of 5.1%. This is an increase in mortality of 2.8% ($p<10^{-12}$).

Patients without any medication error had an average hospital stay of 6.5 days where as patients with medication errors stayed in the hospital for 15.6 days ($p<10^{-15}$).

Figure 3 shows the different medication errors and their frequency excluding patients with no interactions. It shows that most medication errors of table 1 are loop diuretics combined with NSAID, NSAID given together with selective serotonin reuptake inhibitors (SSRI) and angiotensin-converting-enzyme inhibitors (ACE-inhibitors) with NSAID.

On the other side medication interactions concerning dose adjustment in patients with renal impairment did not occur often with the tested substances.

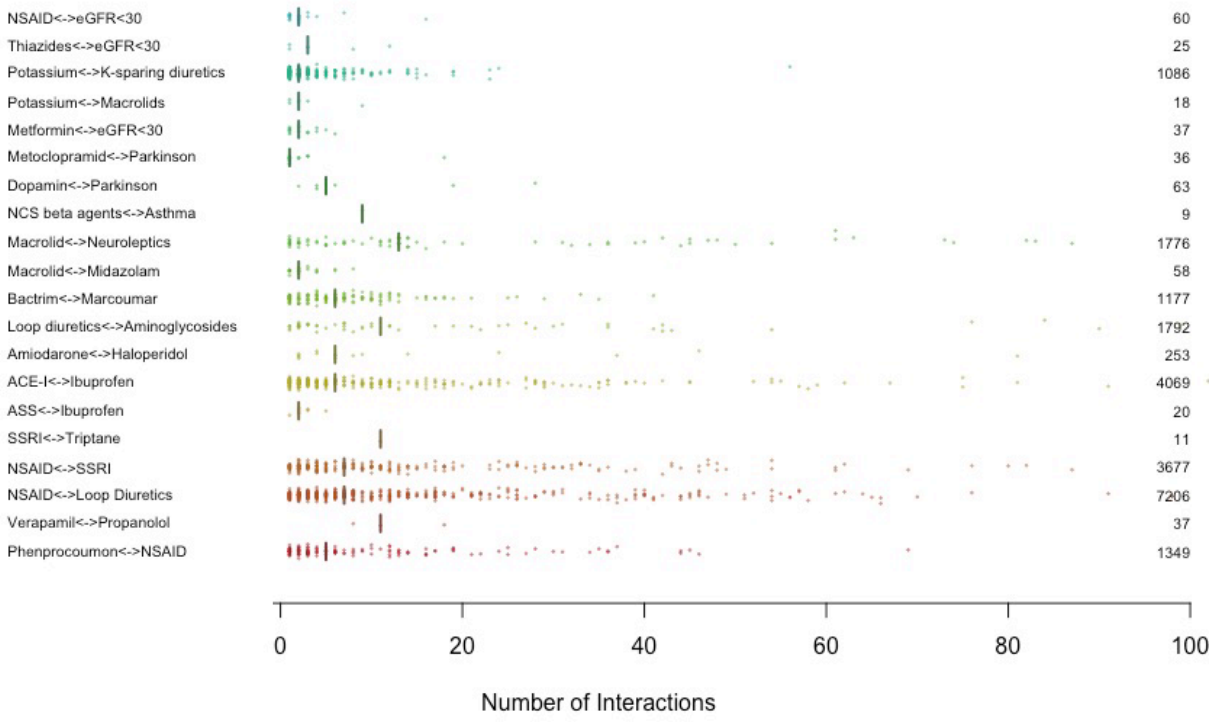

Fig. 3 Total count of individual interactions observed per patients shown relative to the different interactions identified in the data set. Each single point depicts a patient with the quantified interactions; the vertical bar show the median of indidivual interactions per patient. The number at the right border shows the total count of every identified interaction.

It could be concluded that the more diagnoses a patient has and the more medications are taken to treat the diseases, the more likely it is that the higher mortality and morbidity are due to polypharmacy and diseases and not due to the number of drug-drug and drug-disease interactions. Table 2 and the ANOVA (analysis of variance) show a significant effect on the morbidity and can still be observed even if corrected for the number of substances a patient takes. Moreover we developed a linear model, which shows a significant increase of the duration of hospital stay by 0.005337 days ($p<10^{-7}$) by every single medication interaction that occurs within a patient.

Linear model:

*Duration of stay = 0.9 + number of substances * 0.00132 + 0.00534 * number of interactions*

	Degrees of freedom	Sum of squares	F statistic	P - value
Number of substances	1	6537	7716.58	$<2e^{-16}$
Number of interactions	1	17	20.13	**$7.26e^{-6}$**
Residuals	38752	32827		

Table 2 The ANOVA-Table shows that there is a significant influence of the medication errors on the morbidity of multimorbid patients

6. Discussion

6.1. Key findings

As shown in figure 1, patients with a higher number of diagnoses are more likely to have medication errors. With increasing number of diagnoses the number of occurring medication errors also rises, whereas patients with low a diagnose count seem to have less medication errors.

Multimorbid patients with a large number of diagnoses are probably sicker and more likely to suffer from severe consequences than patients that present themselves with just a few diagnoses. So the mortality of those patients will normally be higher and as a consequence, they have to take more medications to cure these diseases. As figure 1 shows, it is more likely to have medication interactions when patients have a high number of diagnoses. Multimorbid patients with many diseases also have a higher mortality rate, so it is not clear what role medication errors play in the mortality rate of multimorbid patients. As the ANOVA in table 2 shows, medication errors have a significant influence on the mortality of the patients, even if corrected for the number of substances.

Medication errors also have an effect on the morbidity patients. Morbidity can be measured with different parameters, a simple surrogate is the duration of the hospital stay. Patients without any medication errors have an average length of hospital stay of 6.5 days whereas patients with one or more medication errors stay in the hospital for 15.6 days on average ($p<10^{-15}$). It also has an effect on the mortality of the patients. Persons without medication errors have a mortality of 2.8% where as patients with more than one medication error have a mortality rate of 5.1% ($p<10^{-12}$). This means that there are patients who die because of medication errors when they otherwise could have survived.

Most medication errors happened when non-steroidal anti-inflammatory drugs (NSAID) were involved. They are often prescribed because of their analgesic and anti-inflammatory effects. They can be used to alleviate pain or against inflammation and fever. Known contraindications for NSAIDs are gastric and duodenal ulcers and known liver and kidney diseases. As NSAIDs are so commonly used for a wide range of treatments it is not a surprise that they are commonly falsely prescribed.

Also an influence of the number of substances taken and the number of medication interactions on the duration of hospital stay was found. We showed that every single interaction increases the duration of hospital stay by 0.005337 days ($p<10^{-7}$). This demonstrates clearly that medication interactions raise the morbidity rate even when subtracting the effects of the basal disease and the number of substances taken.

We could not show an influence of the medication interactions on mortality when corrected for age and number of substances. Probably this is due to the low overall mortality rate of 2%.

6.2. Comparison to other studies

Verbeeck et al (7) did a study about dose adjustment in patients with renal dysfunction and came to the same conclusion, that adverse drug reactions are common in patients with renal insufficiency. Also Calderón-Larrañaga et al (8) came to the result that multimorbidity leads to an accumulation of adverse drug reaction. Other studies such as the study from Buckley et al (9) used a different approach for the detection of medication errors by direct observation of the physicians. This leads to a higher personal effort and an investigator-biased detection system compared to the objective measures of this study because the observers could only see the errors the physicians made and could not specifically search for drugs or diseases that seemed interesting to them. In summon, all of those studies come to the conclusion that adverse drug reactions are a problem in todays' hospital treatment and it should be searched for solutions because those errors can have a significant effect on patients' health.

6.3. Strengths and limitations of the study

The study clearly shows an impact of medication errors on patients' health and their mortality. With the high number of patients included in this study, it can give a representative survey on the effects of these errors. The study does not depend on active surveillance of physicians prescribing medicaments or on patients' subjective side effects. It thus can monitor physicians' treatments objectively and in a very large number. The fact that there is plethora of data provided for each patient makes a solid foundation for more analyses on even more medication interactions with the same approach.

A limiting factor in the significance of the study is that the University Hospital of Zurich is a tertiary hospital and as that, is treating patients that are normally sicker than patients

in a community hospital. So this study with its data represents only the University Hospital of Zurich and the mortality and the number of medication errors can differ from community hospitals. However, a generalization to tertiary hospitals is probably sound, since the effect is clear and the differences in populations small.

It was shown, that the more diagnoses a patient has, the more likely it is that a medication error is present as more drugs to treat the diseases have to be taken. A problem of this study is, that it does not include patient's actual health. When a patient is already severely ill, a medication error could make a bigger difference in the outcome compared to a patient who is young and relatively fit.

When a patient is in great need of a medicament but has a contraindication like high blood potassium or when a medicament that is contraindicated is taken, physicians have to decide whether there is a better solution that prevents a possible medication error, or if they hazard the consequences of the medication interaction. Since this will not show up in our data, a probably false assumption that it was falsely given to the patient is made in this case.

This study only can observe what was documented. Whether or not the right medication had been given has not and can not be studied by our method. Mistakes often happen when medical personal distributes the medicaments, since no data concerning such errors was available to us, further studies are necessary to cover these questions.

6.4. Significance of the study

The results of this study show that medication errors are a problem in today's hospital care. As we just tested a small list of medication interactions, more could be found, if someone looked for even more medication interactions.

Today hospitals, in times of diagnosis-related groups (DRG), tend to keep the patients length of hospital stay at a minimum to reduce costs and to have space for another patient that generates income. Longer hospital stays mean more costs for the hospital. As medication errors extend the hospital stay on average about 9 days, it should thus be in a hospitals interest to keep these medication errors to a minimum out of a solely economic point of view.

Ultimately it is also most important to check every patients medication list for errors because it can have a severe effect on the outcome on his disease. It would be desirable that drug interaction checkers such as for instance www.drugs.com or others would be

considered more often to check the medication lists of patients, because they can give information about the drug-drug-interactions and drug-disease-interactions of a patient. This could keep the medication errors at a minimum. However, at our hospital such a system has been present at the time of the study, so awareness for medication errors has to be improved also.

6.5. Unanswered Questions

To check the influence of the medication errors an interventional study would have to be conducted, which actively reduces the drug-drug- and drug-disease-interactions to find out if the benefit on morbidity and mortality suggested by this study persists also in a prospective study.

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8. Lebenslauf

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Masterarbeit

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Ich bestätige mit meiner Unterschrift die Richtigkeit dieser Angaben.

Datum: 14.11.2016

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