Potential drug-drug interactions in the intensive care

Frequency, clinical relevance and improvement strategy

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CHAPTER 7

| General discussion

This thesis addresses two main topics: 1) potential drug-drug interactions (pDDIs) and high-risk drug combinations (i.e. clinically relevant pDDIs) in patients admitted to the intensive care and 2) computerized decision support systems (CDSS) to reduce pDDI frequency in the same setting. Consequently, the following two research questions have been addressed:

1. What is the frequency of pDDIs and high-risk drug combinations in the intensive care unit (ICU) and which pDDIs are clinically relevant in the ICU setting, in the sense that they require regimen change or monitoring?

2. Does tailoring pDDI alerts to the ICU setting reduce the frequency of administering high-risk drug combinations?

MAIN FINDINGS

Research question 1

The first research question has been answered in Chapters 2, 4 and 5. In our systematic review described in Chapter 2, we contributed to the first research question. In the systematic review, we evaluated the relation between methodological choices in assessing pDDI frequency and the reported pDDI frequency, and formulated reporting recommendation for pDDI frequency studies. Comparison of methodological choices in the reviewed studies showed significant heterogeneity between pDDI frequency studies in ICU patients, and 65% of the studies had a medium to high risk of bias, which complicates the comparison of their findings. Studies with a high risk of bias, small sample size, and use of drug prescriptions instead of drug administrations, were related to a higher reported pDDI frequency, which may overestimate the actual pDDI frequency. To improve comparability of pDDI frequency studies, the reporting quality of studies should be improved. Therefore, we formulated a set of reporting recommendations that extend established reporting guidelines such as the RECORD-PE guideline.[1]

In Chapter 4, we described a Delphi study which was performed to assess clinical relevance of pDDIs in the ICU setting. In total, 148 pDDIs were assessed by a national expert panel of intensivists and hospital pharmacists. For 139 (94%) pDDIs, the experts agreed whether or not they were clinically relevant. Of these, 53 (38%) were considered not clinically relevant in the ICU setting. pDDIs requiring non-standard monitoring, such as therapeutic drug monitoring, were considered clinically relevant more often by the expert panel compared to pDDIs requiring standard monitoring, such as blood pressure monitoring, or measuring blood glucose. Furthermore, most pDDIs that could decrease the efficacy of medication therapy were considered clinically relevant. Also, pDDIs that occur infrequently in the ICU were considered clinically relevant more often, compared to frequent pDDIs. This may be explained by the lack of familiarity of ICU physicians with infrequent pDDIs. Therefore, receiving alerts for such unfamiliar pDDIs, was perceived as relevant.

In Chapter 5, we showed that applying the findings from the Delphi study to ICU data, significantly alters the frequency of pDDIs. The mean number of pDDIs per 1000 medication administrations was 70.1, dropping to 31.0 when only considering clinically relevant ones. On average, ICU patients were exposed to two pDDIs per admission, of which one clinically relevant pDDI. pDDIs occurred mostly on the first day of admission and lasted approximately one day. The same pattern was seen for clinically relevant pDDIs. The most frequent clinically relevant pDDIs were interactions between two QT-prolonging drugs, interactions with digoxin (a cardiac glycoside), and interactions with NSAIDs, thereby increasing the potential risk of cardiac arrhythmias and bleeding.

Research question 2

Chapter 3 described the study protocol for Chapter 4, 5 and 6. The second research question was answered in Chapter 6, in which the results from the Delphi study were put into practice. As previously explained in the thesis introduction, in this chapter we introduced a new term for clinically relevant pDDIs; i.e. high-risk drug combinations, to better capture the meaning of this outcome. That is, exposing a patient to two drugs known to interact, which may result in clinically relevant consequences harming the patient.

In a multicenter cluster randomized stepped-wedge trial in nine Dutch ICUs, we showed that limiting pDDI alerts to clinically relevant ones resulted in a reduction in the number of administered high-risk drug combinations. More specifically, our intervention led to a 10-13% decrease in the number of administered high-risk drug combinations per 1,000 drug administrations per patient, after adjusting for clustering and prognostic factors. In addition, the study showed that the intervention also led to a 6% decrease in ICU length of stay and a 9% increase in appropriately monitored high-risk drug combinations, after adjusting for clustering and prognostic factors.

INTERPRETATION AND MEANING

Reviewing methods for pDDI detection and counting

The results of our systematic review and proposed reporting recommendations (Chapter 2) can support researchers in designing a robust and transparent methodology to evaluate and report pDDI frequency in the ICU. This may contribute to standardization, reproducibility, comparison, and evidence synthesis of pDDI frequency studies, ultimately improving our knowledge about pDDIs in ICU patients and how to address them. Furthermore, the recommendations presented in our systematic review are not only applicable to studies investigating pDDI frequency in ICU patients but can also be applied to hospitalized adult patients, as the recommendations are generic and therefore can be applied to other patient populations, sets of pDDIs and knowledge bases, drug data sources, and detection algorithms.

Clinical relevance of pDDIs

The results of our Delphi study (Chapter 4) indicate that almost 40% of the pDDIs are not considered clinically relevant in the ICU setting. This means that there is room to reduce the number of pDDI alerts shown to ICU physicians, thereby enabling focus on the clinically relevant alerts. Our hypothesis is that by restricting clinical decision support systems (CDSSs) to show pDDI alerts for clinically relevant pDDIs only, alert fatigue will be reduced and more attention will be paid to the remaining alerts. Hence, in our cluster randomized stepped-wedge trial (Chapter 6), we have turned off pDDI alerts for pDDIs considered not clinically relevant in the ICU setting.

Frequency of clinically relevant pDDIs

Our retrospective observational pDDI frequency study (Chapter 5), corroborated the importance of considering clinical relevance of pDDIs. The study revealed a significant decrease in pDDI frequency, from 70.1 to 31.0 pDDIs per 1000 medication administrations per patient, when only clinically relevant pDDIs were taken into account. This substantial reduction illustrates the potential impact of limiting CDSSs to show pDDI alerts for clinically relevant pDDIs only, which would result in a reduction of over 50% in the number of pDDI alerts. Aside from clinical relevance, pDDI duration and timing, contextual information, as well as the presence of other medication related alerts, may be important to consider when tailoring pDDI alerts to the ICU setting.

Focusing on clinically relevant pDDI alerts

Our cluster randomized stepped-wedge trial (Chapter 6) showed that ICU-tailored pDDI alerts significantly reduced the number of administered high-risk drug combinations, improved monitoring, and decreased ICU length of stay. These results demonstrate that by focusing on clinically relevant pDDI alerts only, the alerts become more valuable in terms of clinical impact. This impact manifests in a change in prescribing decisions of intensivists, as they decide to refrain from prescribing high-risk combinations more often, after seeing an alert. Consequently, this prevents ICU patients from being exposed to such combinations. In our trial, this approach resulted in 10-13% decrease in the administration of high-risk drug combination, providing evidence of enhanced effectiveness of the CDSS.

These findings are relevant to clinicians, hospital pharmacists, CDSS developers, managers, quality of care officers, and researchers in the ICU setting. Knowledge about which interactions are clinically relevant in the ICU are transferable to any other type of patient data management system (PDMS) or CDSS than the one we used in our study. We expect that using our list of clinically revenant pDDIs to tailor pDDI alerts to the ICU setting, is beneficial to other ICUs with comparable monitoring options, also outside the Netherlands, as frequently occurring pDDIs and clinically relevant ones are comparable between countries.[2] Furthermore, our results may encourage the tailoring of (pDDI) alerts to other specific settings, such as neonatology, pediatrics or oncology.

In general

Earlier research has shown the potential of CDSSs to help prevent pDDIs, but the overload of irrelevant alerts hampers their effective use.[3-6] The research in this thesis contributed to the current knowledge and understanding of alert relevance and the effectiveness of CDSS. We demonstrated a successful strategy to reduce the number of pDDI alerts and improve CDSS effectivity. We showed that a CDSS that only provides clinically relevant pDDI alerts can decrease the exposure to high-risk drug combinations in ICU patients, and lead to improved pDDI monitoring and a shorter length of stay in the ICU. Improving the fit between drug safety alerts and patient setting, in order to improve CDSS effectivity, may be successful in other patient settings as well.

Reducing the exposure to high-risk drug combinations may help prevent adverse drug events, thus enhancing patient safety in the ICU. Improved monitoring of the potential adverse effects of pDDIs helps intensivists to detect problems early and prevent or preclude further harm, leading to better patient outcomes. Outcomes such a shorter length of stay in the ICU have several benefits, such as improving the patient's comfort and quality of life, more capacity with the same number of beds, and reducing costs. For intensivists, it would be valuable to have an efficient and effective CDSS helping them make safer medication decisions, instead of having a CDSS producing many irrelevant alerts costing time and attention.

Our adapted CDSS led to a 10% decrease in the number of administered high-risk drug combinations. This might raise the question whether there was more room for improvement. On the one hand, it would not be feasible to reduce the number of high-risk drug combinations to zero, as ICU patients might need both drugs involved in a high-risk drug combination to survive, despite the risk of harm. Hence, the goal should be to avoid administration of high-risk drug combinations if possible, and otherwise to prescribe the combination while being aware of the potential consequences and adequately monitoring those. On the other hand, to reach this goal, we only addressed one factor influencing alert fatigue and CDSS effectivity, namely alert relevance. By addressing more of those factors such as efficiency, ease of use and usefulness, CDSS effectivity could be further optimized.[7]

COMPARISON TO THE LITERATURE

The proportion of pDDIs that was considered clinically relevant in our Delphi study is in line with findings from similar studies in which a Delphi procedure was used to assess clinical relevance of pDDIs.[8,9] Regarding pDDI frequency, other studies report one to five pDDIs per ICU admission, and overall, 58.0% of ICU patients have a pDDI.[10] Consistently, in our frequency study we found on average 2 pDDIs per admission, of which one clinically relevant, and 53.8% of all patients having a pDDI. We found one other study that investigated the frequency of clinically relevant pDDIs in a single ICU. They found on average 1.7 clinically relevant pDDIs per admission, slightly higher compared to our findings. Differences in clinical relevance definition and pDDI detection method could explain this. Another possible explanation could be the

longer ICU length of stay in their study population (1.7 vs 1.0), which was probably due to a smaller proportion of elective surgery admissions. Regarding pDDI duration and the moment of the pDDI, we found no other studies that reported these outcomes.

With regard to the intervention study described in Chapter 6, to the best of our knowledge, no other studies evaluated the effect of tailoring pDDI alerts to the ICU setting on the administration of high-risk drug combinations in the ICU. In their review on CDSS-based interventions to improve medication outcomes, Shahmoradi et al.[11] state that there has not been much research on the impact of CDSS on patient outcomes and that more research is needed in this area. One study outside the ICU found that optimizing CDSS by six optimizing strategies (including alert design, patient specific alerting and customization of the CDSS knowledge base) resulted in a higher acceptance rate of pDDI alerts and thereby reduced administration of pDDIs, indicating less exposure to pDDIs.[12] In addition, there are studies, set outside the ICU, that evaluated the effect of optimizing CDSS drug alerts on alert frequency, alert compliance and time spent on assessing alerts. Alert acceptance or compliance means that the prescriber adheres to the action recommended by the alert. However, the outcomes of those studies are process outcomes and did not directly measure the effect of an intervention on actual patient exposure to high-risk drug combinations.

Specifically, Helmons et al.[13] report that suppressing clinically irrelevant pDDI alerts resulted in a 74% decrease in the number of pDDI alerts for prescribers and 45% reduction in time spent on pDDI alert checking by pharmacists. In this study, clinical relevance was evaluated by an expert panel. Kawamato et al.[14] report that by reviewing and optimizing CDSS content, the number of drug alerts was reduced by 19.8%, and the proportion of alerts leading to a discontinuation of the triggering drug within one hour was increased by 16.9%. Parke et al.[15] report that recategorization of severity levels of pDDIs alerts by an expert panel decreased alert overrides by 6%. Paterno et al.[16] showed that tiering alerts by severity led to a higher DDI alert compliance. In this study, severity levels were assigned by pharmacists and physicians. Wasylewicz et al.[17] showed that customizing pDDI alerts by incorporating contextual information considerably decreased the number of irrelevant pDDI alerts. In this study, clinical relevance was defined as an alert intervened upon by a pharmacy professional.

Although all outside the ICU, these results show, similarly to our study, that optimizing CDSSs and their alerts is needed to improve and maintain CDSS effectivity. This need is even more pressing, considering that modern EHR systems with built-in CDSSs, have the capability to generate alerts not only for medication safety risks, but also for a wide range of other purposes. These systems can be (mis)used to alert for various tasks including to complete checklists, conduct lab measurements, check for allergies, change IV lines, assess pain or delirium scores, and so on.[18]

STRENGTHS

The research in this thesis has several strengths. First, our systematic review was the first study to analyze sources of heterogeneity that influence the measured pDDI frequency and aimed to improve reporting of pDDI detection methods. Second, our findings were translated into reporting recommendations which can be used in practice as an extension to the RECORD-PE guideline.[1] Third, our hypothesis that showing alerts for clinically relevant pDDIs only would improve CDSS effectivity, and lead to a decreased the number of administered high-risk drug combinations, was founded on previous literature[5,19-22] and a theoretical framework, i.e. Reason's model of accident causation for drug-safety alerting.[21] Fourth, the Delphi procedure we used to evaluate clinical relevance of pDDIs in the ICU setting is a rigorous method in which opinions from experts are gathered anonymously. The live meeting, conducted to address any disagreements, allows for reflection and change of opinion where necessary.[23] Studies on the topic of pDDI frequency in the ICU sometimes mention the frequency of clinically relevant pDDIs, but often their definition of clinical relevance is based on severity levels of pDDIs stated by a pDDI knowledge base such as Lexi interact or Micromedex.[2,24-27] The Delphi method is a more rigorous method to establish clinical relevance, especially for a specific setting such as the ICU. Fifth, the inclusion of future users of our adapted CDSS (MiM+) in the Delphi process, could have enhanced the acceptance of the adapted CDSS in our intervention study.[28]

Sixth, in the Delphi study (Chapter 4), the frequency study (Chapter 5) and the intervention study (Chapter 6), we reused routinely collected data from the PDMS. Therefore no additional registration of data - and therefore registration burden - by our participating ICUs was required. Seventh, in both the frequency study and intervention study, a large sample of ~100,000 and ~10,000 patients respectively, was included from multiple centers, representing various ICU types, and a heterogeneous population of ICU patients. This contributed to greater statistical power, more precise estimates, improved generalizability and validity of our findings. Eighth, for our intervention study, we used a cluster randomized stepped-wedge design, which is a strong design comparable to an randomized controlled trial design. [29] In both the frequency study and the intervention study, we used medication administrations instead of prescriptions to detect pDDIs. Most studies on pDDI frequency used prescriptions, but our approach ensured that patients actually received the medication and allows for a more accurate measure for pDDI frequency.

Last, in both the frequency study as the intervention study, we used multiple and diverse outcome measures, which increased robustness, validity and generalizability of the results. For instance, in the frequency study we used several secondary outcomes to enable comparison of our results to other studies, including the number of pDDIs per patient and the proportion of patients with at least one pDDI. By evaluating the duration and moment of pDDIs as well, we provided a more nuanced understanding of pDDIs in the ICU setting. In the intervention study, besides evaluating the effect of our adapted CDSS on the administration of high-risk drug combinations, we evaluated the effect on pDDI monitoring and length of stay, and found

an effect on all three outcomes. This strengthens the findings, and shows that a reduced number of administered high-risk drug combinations and improved monitoring in cases when avoiding the combination is not possible, also is associated with a shorter ICU length of stay. The shorter ICU length of stay was not due to mortality, as ICU mortality was similar between the control and intervention group when corrected for relevant confounders such as disease severity. Furthermore, we showed that restricting alerts to clinically relevant ones, had an effect on the prescriber's behavior beyond whether they prescribed the interacting drugs, as the monitoring of pDDIs improved as well. For example, in the case of a high-risk drug combination consisting of two QT-prolonging drugs, intensivists ordered an ECG more often.

LIMITATIONS

The research in this thesis also has limitations. First, the Delphi method is based on expert opinions of intensivists and hospital pharmacists, which are inherently subjective. However, the participating experts have considerable pharmacotherapy expertise and experience in the ICU and represent both teaching and non-teaching ICUs from fourteen different ICUs with various patient populations. It must be noted though, that in the questionnaire and during the live consensus meetings the current evidence on pDDI mechanisms per interaction was shown. Second, in our Delphi study, we did not assess all pDDIs. However, the pDDIs that were not assessed were both infrequent and considered less severe according to the G-standard. Also, it is the frequent pDDIs that cause the bulk of, quite often irrelevant, pDDI alerts. Therefore, to have the largest effect, it is mainly important to know which of the frequently occurring pDDIs are considered not clinically relevant in order to reduce alert fatigue. Third, our pDDI detection algorithm, that is used in both the frequency study and the intervention study, did not consider the half-life of medications. This might lead to an overestimation of pDDIs involving medications with a short half-life and an underestimation of pDDIs involving medications with a long half-life. However, incorporating half-life would only partly address the issue of how defining the overlapping period of two drugs when assessing pDDI frequency. Other drug characteristics such as dose, frequency, duration of exposure, as well as patient characteristic such as renal and liver function and mechanism of drug interactions (e.g. via liver enzymes activity induction or reduction), may also influence drug elimination and clearance from the body. These factors therefore may also affect the timeframe during which drugs may interact. Given this very complex interplay of factors, defining a pDDI as the administration of two interacting medications within a 24h period, as done in this thesis, is a practical and reasonable alternative. Fourth, we did not investigate other important factors that influence alert fatigue, such as alert timing or design. However, this does not diminish the effect that improving clinical relevance of pDDI alerts had on CDSS effectiveness. All ICUs participating in the intervention study had the same alert timing and design. Fifth, our intervention study was conducted with only one CDSS, i.e. MiM. Nevertheless, the list of drug combinations that are perceived as high-risk in the ICU is transferrable to other CDSSs and PDMSs. Last, we did not measure the effect of our tailored CDSS on patient harm related to clinically relevant pDDIs. Assessing whether patient harm occurred due to medication or, in our case, clinically relevant

pDDIs, requires comprehensive manual patient chart review and causality assessment by medical experts.[30] Although such a procedure would be valuable to conduct, given the labor and time-intensive nature of the procedure, it was beyond the scope of the intervention study. However, it is to be expected that a reduced exposure to high-risk drug combinations will lead to less patient harm consequently.[31]

UNINTENDED RESULTS

Besides the results that we intended to find, we found some unintended results which are worth mentioning. In the frequency study, we found that around 42% of the patients is discharged with a pDDI, of which the majority were interactions between two QT-prolonging drugs and interactions potentially leading to disturbances in blood pressure, potassium or glucose. According to literature, medication errors are common at the moment of ICU discharge to a hospital ward, and occur in more than 50% of the ICU patients.[32] Alerts could be triggered upon ICU discharge, or the risks could be shared with the relevant caretaker, to secure a safe transfer from the ICU to non-ICU wards and help physicians there to take appropriate monitoring actions where necessary. Especially since non-ICU wards do not monitor vital signs continuously.

In the Delphi study during the live consensus meetings, experts mentioned that besides using CDSS, they used other measures to reduce DDI-related risks. For example, some ICU experts refrain from using medication classes with interaction potential, such as vitamin K antagonists and NSAIDs, to prevent interactions with these medication classes. Consequently, this means that alerts for these pDDI will not be triggered. In case of refraining from NSAIDs, intensivists do not follow the sequence of the WHO pain treatment steps[33], they skip the NSAIDs, and prescribe opioids. This undesirable 'shortcut' could be avoided when CDSSs would support intensivists by providing safe alternative treatment options to reduce the administration of potentially inappropriate medications.

FUTURE RESEARCH

To improve CDSS effectiveness to a greater extent, pDDI alerts could be improved further. The two-stream model provides a classification of factors contributing to the success or failure of CDSSs.[34] The model consists of two categories for evaluating the effectiveness of CDSSs: the clinical stream and the cognitive-behavioral stream. The clinical stream is about using clinical knowledge to reach a conclusion ("what is true"), which can be used for a decision or advice ("what to do"). In the clinical stream, the quality of the advice provided by the CDSS is evaluated. The cognitive behavioral stream is about how the advice is presented to the physician, and how the physician is affected by the advice. In the cognitive-behavioral stream, alert adherence or acceptance, or other process indicators serving as intermediaries of clinical outcomes, are evaluated.

With regard to the clinical stream, one strategy to further improve the quality of pDDI alerts could be to personalize alerts by incorporating specific patient risk-factors such as comorbidities or impaired kidney function [35,36] This would also be in line with the recent changes to the G-standard, that introduced clinical rules incorporating patient factors, to enable more contextualized medication surveillance. In Dutch, those clinical rules are referred to as 'Medisch Farmaceutische Beslisregels'.[37] Contextual information can include patient characteristics such as present risk factors, dynamic patient information such as lab results, and information on the mechanism of the pDDI. For example, for frequent pDDIs such as QT-prolonging drugs interactions, an alert could only be triggered if risk factors such as older age, female gender, heart disease history, electrolyte abnormalities and impaired kidney function are present.[35] For interactions with NSAIDs and corticosteroids, alerts could be suppressed if the risk of harm is already mitigated by co-medication, i.e. a proton pump inhibitor. There has already been a study in the Netherlands that shows the contextualization of pDDI alerts can decrease the number of alerts.[17]

Another topic for future research regarding the clinical stream, would be to take into account the half-life of drugs, drug dose, and pDDI duration. It could be valuable to incorporate these factors in CDSSs as well as in the methods used for detecting and counting the number of pDDIs. These factors are important for actual DDI manifestation because as pharmacokinetic/pharmacodynamic mechanisms are often time dependent. Not taking into account the half-life of drugs, for example, leads to an overestimation of pDDIs involving drugs with a short half-life, and underestimation of pDDIs involving drugs with a long half-life.

With regard to the cognitive-behavioral stream, Westerbeek et al.[7] found that the most important barriers and facilitating factors for acceptance of alerts from medication-related CDSSs are relevance, efficiency, ease of use and usefulness of the CDSS. For example, showing redundant alerts is not useful, a very slow CDSS does not save the prescriber time and is not efficient, and a system that requires many clicks is not easy to use. We believe that the ability to modify the dosage of drugs or initiate monitoring actions directly from within the pDDI alert window would improve efficiency and advance ease of use, and could result in improved monitoring. Also, timing of the alert is important; if placed well in the thought and decision process of the prescriber, it could improve efficiency.[20]

It would be valuable to evaluate patient harm associated with pDDIs in the ICU. According to Fitzmaurice et al., few studies investigated that topic.[10] As mentioned earlier, manual patient chart review and causality assessments are very labor and time intensive.[30] Therefore, measuring patient harm due to pDDIs as an outcome in studies on CDSS effectiveness, is rarely seen.[11] According to a recent systematic review on DDIs in hospitalized patients, around 10% of hospitalized patients experience a clinically manifested DDI, which they defined as DDIs with clinical implications that were confirmed by laboratory tests and/or signs and symptoms documented in the medical record.[38] Possibly, using triggers tools to pre-select patients for manual patient chart review, may decrease the time needed to assess causality between

pDDIs and patient harm. [39,40] This strategy may be valuable to gain more insight into the clinical consequences of pDDIs in the ICU setting. Finally, as new medications are being developed continuously, new pDDIs arise, of which we do not know the clinical relevance to the ICU setting. Also, new findings regarding interaction potential of existing drugs may become available, and technical possibilities of CDSS may evolve over time. Therefore, to remain current, it would be important to evaluate the clinical relevance of new pDDIs in the ICU on a timely basis and make the results known, so ICUs can implement the results in their CDSS.

CONCLUSION

The research in this thesis contributed to a better understanding of pDDI frequency in the ICU, their clinical relevance in this setting, and CDSS effectiveness. Of the pDDIs included in the G-standard, almost 40% are considered not clinically relevant in the ICU setting. Still, ICU patients are frequently exposed to those clinically relevant pDDIs, i.e. high-risk drug combinations, which may result in patient harm. Therefore, the use of CDSSs to warn intensivists for high-risk drug combinations is warranted. This thesis shows, that to gain most from CDSSs, tailoring them to their clinical context should be considered before implementing them. The use of ICU-tailored pDDI alerts reduced the number of administered high-risk drug combinations, improved patient monitoring, and decreased ICU length of stay. Further strategies to optimize CDSS effectivity could be achieved by addressing additional factors related to the clinical and cognitive-behavioral stream that influence alert fatigue and system acceptance.

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