Potentially Preventable Hospital Admissions Related to Medication

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Chapter 7

General discussion and future perspectives

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This thesis shows that (potentially preventable) hospital admissions related to medication ((PP)HARMs) are still frequently occurring in the Netherlands. The good news is that the numbers remain stable between 2008 and 2013[1]. Together with increasing complexity of healthcare and an ageing population, this may imply that improvements have been achieved[2, 3]. This could be the result of efforts taken by healthcare providers to prevent PPHARMs. However, after the first Dutch studies looking into hospital admissions related to medication, the ambition was expressed to reduce the numbers and unfortunately this decrease is still pending. These first studies were initially published as study reports (in Dutch[4]) in 2006[4, 5]. They described the number of admissions caused by medication in general and inappropriate medication use in particular. In response to the reports, the Ministry of Health of the Netherlands organized a Ministerial Action Plan Safe Healthcare. This entailed a number of initiatives including the establishment of a taskforce consisting of different types of healthcare providers especially assigned to compose recommendations to reduce the number of HARMs in the Netherlands. They prepared 40 recommendations based on the previous two studies[6]. Since then, there have been multiple initiatives to reduce the frequency of (PP)HARMs. In order to determine the number of PPHARMs more efficiently the Ministry of Health issued a follow-up study in 2012 where the Quick Assessment of Drug-Related Admissions over Time (QUADRAT) method was developed and used to calculate the number of (PP)HARMs in 2005 and 2008[7]. The study showed a small non-significant decrease in numbers between these years. However, the recommendations were not yet published and the effect of it was therefore not measurable. The authors also indicated that a follow-up study should take place later in time. This follow-up study was issued by the Ministry of Health aimed at determining the frequency in the years 2008, 2009, 2011 and 2013, using an adjusted version of the QUADRAT method.

Stable, but shifting

Although the frequency of (PP)HARMs is stable, our results also show that the types of PPHARMs have changed in comparison to previous research. In the QUADRAT study serious gastro-intestinal (GI) events were the most frequently occurring PPHARMs followed by fractures and heart failure[7]. However, in our study fractures were the most frequently occurring type of PPHARM followed by syncope/dizziness/hypotension/collapse and GI-complications[1]. This

shows GI-complications are no longer the most frequently occurring problems. Most of these GI-complications concerned gastro-intestinal bleeding and/or ulcers caused by NSAIDs or acetylsalicylic acid, which may be prevented by adding a gastroprotective agent in patients at risk[8]. This preventive measure was one of the recommendations of the HARM wrestling report and relatively easy to implement [6]. As is shown in the study described in chapter 4 the adherence by healthcare provider to this recommendation increased between 2009 and 2014, which may have contributed to the solution of the problem. This study also showed that the adherence to the recommendations surrounding fractures due to fall incidents remained unchanged and still had moderate and major room for improvement. The fractures in patients of 65 years and older were most often caused by benzodiazepines and opioids. These are both drugs which are advised against in the elderly because of the increased fall risk[9, 10]. However, according to the GIP-databank (Medicines and Aids Information Project) 34% of all benzodiazepine and 44% of all opioids users are 65 years or older[11, 12].

The HARM wrestling recommendation on reduction of falls caused by benzodiazepines was to have a consultation with the patient two weeks after start of the benzodiazepine and – when chronic use is impossible to avoid - annually. For the indicator study, this was operationalized as the number of consults between patients and GP's, two weeks after start of benzodiazepines and annually. Therefore, this indicator did not include whether the consult was used to discuss the benzodiazepine use, most likely leading to an overestimation. On the other hand, the number of (PP)HARMs caused by benzodiazepines is most likely also overestimated. The causal association was estimated based on the information provided in the discharge letter. The assessors used the algorithm of Kramer[13] to asses this causal association, but this algorithm depends on the information available in the discharge letter. Especially the orthopedic discharge letters did not include a lot of information discussing the cause of the admission leaving assessors to answer question 2 of Kramer's algorithm (Is the drug the only potential cause for this event?) with "Yes". Yet it is well-known that the occurrence of falling is most often multifactorial[14]. Nevertheless, the implementation of consults after prescribing benzodiazepines appears to be low. This may be explained by the relative complexity of the intervention: it takes extra time for the doctor, especially comparing to a simple prescription of a gastroprotective agent. Furthermore, pharmacists can monitor the prescription of a gastroprotective agent, but cannot monitor whether the consultation after two weeks is conducted. Therefore, the best way to prevent these types of admissions is by not prescribing these drugs to elderly patient at all.

And if necessary, only for a short term with a pre-set stop date and under strict supervision. This is further emphasized by the World Health Organization who has dedicated a fact sheet to this subject including the recommendation to reduce or withdraw the use of psychotropic drugs by elder people[15].

As mentioned before, fractures are not only caused by benzodiazepines, but also by opioids. It is well-known the world is in an opioid epidemic causing an alarming increase in opioid-related morbidity and mortality[16, 17]. In the study described in chapter 4 opioids are most often associated with a PPHARM causing not only fractures, but also syncope /dizziness /collapse and ileus/constipation. The HARM-Wrestling recommendations included a specific recommendation to prevent constipation by adding a laxative to the opioid regimen. However, as is shown in the study in chapter 5 the adherence rate was only 54% (ranging between 18 and 88%) demonstrates this recommendation remained unchanged between 2009 and 2014 and still had moderate room for improvement. In chapter 6 the reason GPs have for not co-prescribing a laxative was further investigated. No relation was found between the reasons for non-adherence to the guideline and actual lack of co-prescribing. A main reason for non-adherence is that patients refuse a laxative, which could be the focus of future interventions. This was also found in another study which found that one in four patients did not use a laxative alongside the opioid with the main reason being that either the prescriber or patient did not consider them necessary while the prevalence of constipation in this same study doubled during opioid use[18]. Patients (and prescribers) should be well informed about this side effect and the question is whether this is the case when patients refuse to use a laxative. The patient should be optimally informed of the reasons why taking a laxative is important. Only after optimal information, shared decision making on the use of a laxative can be performed which may lead to increased guideline adherence.

The HARM-Wrestling recommendations did not include recommendations on the prevention of fractures and syncope /dizziness /collapse by opioids. Based on the results of our studies, such recommendations need to be drafted and therefore we recommend to draft a revised set of HARM wrestling recommendations, excluding the recommendations that are no longer necessary given the high degree of implementation and including recommendations for new problems. Specifically for fractures and syncope/dizziness/collapse by opioids, such new recommendations should be seen in the light of the problem of the opioid epidemic and should thus be focused on.

Another way to reduce the number of opioid-related hospital admissions is by strict monitoring of opioid prescriptions. In the Netherlands the WHO pain ladder is implemented where an opioid is only considered in addition to other non-opioid analgesics[19]. This follows a step-up methodology where the next step is only prescribed if the previous step failed to be effective, so opioids are only prescribed when non-opioids are insufficient to reduce pain. However, there are circumstances when a direct switch to the opioid step is acceptable, for example post-surgery[20]. Pain management is then a priority and patients are prescribed opioids. In the Netherlands postsurgical pain management is an indicator for the quality according to the Health and Youth Care Inspectorate. This is to encourage healthcare providers to pay extra attention to this topic[20]. However, there are no clear recommendations regarding pain management after discharge from the hospital and how long pain medication should be continued. This leads to prescriptions being repeated by general practitioners as was shown by Aalouch et al[21]. This case-control study including 1203 patients demonstrated that 23% of patients receiving postoperative oxycodone refilled their prescription after discharge. This could result in chronic opioid use and may therefore contribute to the opioid epidemic. Bao et al. demonstrated that implementation of a Prescription Drug Monitoring Program can lead to a 30% reduction in the rate of prescribing so-called 'Schedule II opioids' (category with the highest potential of abuse and dependency)[22]. This type of monitoring thus not only contributes to reducing the opioid epidemic, but may in the end also lead to a reduction in PPHARMs.

The female sex

Alongside the shift of the type of PPHARMs the risk factors could also have changed in time. In Chapter 3 and 4 of this thesis the risk factors of PPHARMs were further investigated. These studies demonstrated that age and polypharmacy are the most stable risk factors of PPHARMs. This further underlines the focus of improvement measures on the elderly with polypharmacy. That elderly are more prone for PPHARMs is expected since they are less healthy, have more comorbidities and use more medication. They should therefore be monitored more closely. Interestingly female sex was not a stable risk factor in the systematic review in Chapter 3, but was significantly associated with PPHARMs in the study described in Chapter 4. Female sex as a potential risk factor is complex. It is well-known that differences between sexes and gender can lead to differences in pharmacokinetics, resulting in differences in pharmacodynamics[23, 24]. Our knowledge about the diagnosis, treatment, and prevention of diseases originates primarily from data derived from human-, mammalian-, and cellular models, that have been based on the male

sex or did not include sex as a variable at all [25-27]. The U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have introduced initiatives in an effort to include females in clinical research, after which the inclusion and distribution of both genders have become more even[26, 28-30]. Nevertheless, the bias toward the male sex in the past decades has led to a disparity in basic and translational research[27]. This is in line with reviews on the adverse event reporting systems stating that females generally report more adverse events than males[23, 31, 32]. To fully understand the effects of sex on PPHARMs more research into sex related aspects of pharmacokinetics and pharmacodynamics is needed.

As chapter 4 studied risk factors of PPHARMs further research is also necessary as to why sex would be a risk factor of preventable hospital admissions. This association could suggest that healthcare professionals more often deviate from guidelines in females compared to males. Several studies confirm that females are indeed treated differently than men[33, 34].

Methodological considerations

QUADRAT analysis

In chapter 2 the prevalence and incidence of (PP)HARMs were determined. To select a potential HARM, the HARM+list was used. This list made it easier to find a HARM as only two admissions had to be assessed to find one case which is more efficient in practice. This list was constructed by using the adjusted QUADRAT method. The QUADRAT method uses a Gamma Poisson Shrinker (GPS) [35] and trend analysis to calculate a gross pharmacologically plausible drug-event association. In the GPS-analysis all drug-event combinations which occurred more often than expected were selected. The next step was the assessment by a physician and pharmacist. They assessed whether the combination was based on a possible adverse drug event. If the drug was given to prevent the associated admission it was excluded, since the admissions was most likely not caused by the drug but rather by the lack of effect of the drug. In addition, there were cases in which a combination occurred more frequently than would have been expected but was excluded because no evidence was found to suggest an adverse drug event. By excluding these combinations potential unknown side effects were excluded as well. These result could have given us more insight on potential unknown adverse drug events and should therefore be included in future research using this methodology.

Additionally, the QUADRAT analysis was further adjusted in our study by including a Self-Controlled Case Study[36]. This was done in order to extract potential confounding (i.e.

comorbidities) by letting the patient itself being its own control. However, this led to the exclusion of only one association. The contributing value of this additional measurement was therefore limited and should be considered to be excluded in future research.

The method used to calculate the prevalence of (PP)HARMs is quite ponderous and needs a lot of data to calculate the gross and net prevalence. To make close monitoring more accessible and more frequent a predictive methodology should be developed. The positive predictive value of the QUADRAT study and our study were comparable with 51.2 (95% Confidence Interval (CI):50.5–51.9%) and respectively 59.3% (95%CI: 56.7%-61.9%) for causality. This higher result is because of the stratification by age in our study. If the younger group was used the mean PPV would have been around 52.5%. Using the HARM+list and this estimated PPV a more deployable method could be developed.

Assessment of causality and preventability

After the construction of the HARM+ list a sample was taken from the PHARMO-DHD-database. Causality and preventability were then assessed by a physician and pharmacist. The assessment of causality was done by using Kramer's algorithm[13]. By using these six questions the potential association between the drug and the event was assessed. However, not all six questions could always be answered because of lack of information. The assessors were given the medication profile of the patient (showing the drug use prior and after the event) and the discharge letter sent to the general practitioner. However, the discharge letter was not always sufficient to answer the questions on overdose, dechallenge and rechallenge. The assessors did have the possibility to not assess the admission if there was not enough information, but this was only done in cases with severe lack of information.

The algorithm of Kramer results in total scores, which are translated into the following outcomes regarding the causal association: definite, probable, possible or unlikely[13]. Given the uncertainties due to lack of information, we restricted the outcomes to possible and unlikely, because probable and definite cases were rare. Given the limitations of Kramer's algorithm, we need better ways to assess causality in these types of epidemiological studies. A potential solution may be offered by better documentation within hospitals. Although doctors know that a hospital admission is medication related, they rarely document it that way using the specific disease codes. Another solution may be the use of artificial intelligence using free text algorithms to identify medication related hospital admissions.

The interrater agreement between physician and pharmacist was low with a kappa value of 0.24 and 0.26 for causality (stratified by age-group) and 0.21 and 0.22 for preventability[37]. However, this interrater agreement is solely based on the outcome of the algorithms (causal: yes/no ; preventable: yes/no). The assessors could assign a drug to the admission which they deemed the causative drug. Whether this drug was the same for both assessors is not determined and was therefore not included in the interrater agreement. Therefore we expect this interrater agreement was overestimated. In a previous study conducted by the same research group a higher kappa value was found, but was still low[7]. One of the goals of this study was to increase the interrater agreement. That is why the researchers educated the assessors in two sessions on how to assess an admission and in which way they should deal with lack of information. However, this has not led to an increase in kappa value. This shows how hard it is to assess the causality and the preventability.

As mentioned previously, the discharge letters often lacked the information needed to perform a correct assessment. Especially letters from the orthopedic ward were very brief. They often did not include any information on the cause of the fracture, but only mentioned the treatment of the surgery in a concise manner. But also other wards had admissions with brief information. This is of course not favorable for this type of research, but also general practitioners cannot use the discharge letter for further adjustment of the treatment. A way to improve these letters is by standardizing these types of letters with at least basic information of the admission and treatment given in the hospital. This may help to prevent readmissions[38].

Future perspectives

The studies in this thesis show that PPHARMs still frequently occur and thus better implementation of improvement measures is needed, as well as the development of new improvement measures for the newly identified issues.

As adherence to recommendations to reduce the number of (PP)HARMs is still too low for certain recommendations, efforts to improve implementation are needed. A way to do this is to provide healthcare professionals with regular feedback on their adherence. This knowledge could help them to adjust their behavior. Using the developed indicators a built-in adherence system in the GP information system could give direct feedback and a regular rapport can then be extracted to monitor the improvement . However, adjusting such a GP information system is

complicated, so other ways of implementation need to be explored as well, for example by using the expertise of the pharmacist.

Patients should be empowered in order to increase their motivation to take preventive measures, as was seen from the study on the reasons not to prescribe laxatives in opioid users. Better information and education may help to achieve this. It is especially important the patients receives consistent information, and therefore healthcare professionals need to harmonize their information. Patient journeys could be developed to define clear responsibilities and may thus aid in preventing conflicting information. Furthermore, these patient journeys enable to provide the information that is really needed, as the need for information varies between patients.

When assessing the discharge letters the assessors noticed that many of the (PP)HARMs were not identified by the healthcare provider as such. The event was treated, but the drug was continued without consideration, which could cause readmission[39]. Therefore the identification of a PPHARM is crucial. The HARM+list reduces the number of admissions to assess to find one (PP)HARM to two admissions. This means this list is effective in finding a potential (PP)HARM. This list could therefore be used in practice to trace potential (PP)HARMs which could lead to preventive measures, especially when identification can be performed automatically in the hospital electronic patient record system (e.g. by using text mining)[40].

As mentioned before the lack of effect of the drug was excluded. However, this could give insight into other potential (PP)HARMs, since lack of effect could also be considered as a hospital admission related to medication. Future research should establish scope of this problem, as well as potential reasons such as non-adherence.

As mentioned, multiple initiatives were taken to reduce the number of HARMs. An example is the medication review. This intervention performed by the pharmacist and general practitioner with cooperation of the patient is performed in high risk patients with polypharmacy. This intervention has been proven effective in reducing the number of drug related problems and improving the quality of life[41], but still has not been proven effective in reducing the number of HARMs[42]. When selecting patients eligible for a medication review the Dutch guideline used to focus on certain risk factors such as age, polypharmacy (five or more drugs), number of comorbidities, renal function, cognitive impairment, high fall risk and living situation (dependent/independent). These were all risk factors significantly associated with HARMs in the study performed in 2006[4]. However recently the guideline has changed to old age, hyper-

polypharmacy (10 or more drugs), frailty or at a time of risk (i.e. hospital discharge). Especially frailty remains hard to define, but is seen more as an accumulation of potential risk factors. The healthcare provider therefore has to assess whether the patient needs a medication review. Targeted risk factors to identify these patients are therefore needed. Our studies revealed that such risk factors are difficult to identify. Risk factors also do not appear to change over time, while this would be expected when certain improvement measures have been fully implemented. For example, by exchanging renal function parameters, community pharmacists could improve the quality of dosing in renal failure, leading to less PPHARMs related to renal function[43, 44]. Yet, we did not see this in our study on the trends in risk factors. Therefore, future studies on risk factors and better ways to identify them are still necessary.

Conclusion

Since the first Dutch studies on medication related hospital admissions, many measures have been developed to reduce their frequency. The studies in this thesis show however that this frequency is still high and that many measures are not well implemented. Better implementation, the development of new measures, patient empowerment and automated monitoring with help of artificial intelligence are needed to finally achieve the goal the Ministry of Health formulated after the first studies: a reduction of 50%.

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