Pharmaceutical care by clinical pharmacists in patients with musculoskeletal disease

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Chapter 7

General Discussion

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Worldwide healthcare budgets are under pressure. Although overall healthcare expenditures increase, focus lies on improving quality and efficiency of care. There is much room for improvement since medication errors occur frequently; in The Netherlands an estimated 19,000 drug-related hospital admissions occur yearly, which could have been prevented[1]. This is probably the tip of the iceberg. Moreover, in hospitals medication errors lead to adverse outcomes. Especially frail elderly are prone to developing adverse outcomes of drug therapy. Therefore much effort has been put into the development of clinical pharmacy services. It has been shown that clinical pharmacy services can reduce mortality, morbidity and costs[2-4].

Musculoskeletal disease is a collection of various diseases. Rheumatoid arthritis, osteoarthritis and osteoporosis are diseases with a high burden considering loss of quality of life. In The Netherlands yearly more than 80,000 fractures occur and the incidence of knee- and hip replacement is estimated to be 19,000 and 10,500 per year, respectively[5].

Although in the United Kingdom the speciality "orthopedic pharmacist" is acknowledged[6] only few studies focused on the impact of clinical pharmacy services in patients with musculoskeletal disease.

The overall aim of this thesis was to assess the added value of clinical pharmacy services in patients with musculoskeletal disease. Two major areas of interest were selected: improving the treatment and prophylaxis of corticosteroid-induced osteoporosis (CIOP) and enhancement of medication safety through peri-operative drug management in major orthopedic surgery. The research questions that we formulated were:

1. What are the global trends in prevention of CIOP and what interventions strategies are possibly effective?
2. What is the baseline longitudinal patterns in prophylaxis of CIOP in our region?
3. What are the major barriers to the prescription of adequate CIOP prophylaxis?
4. Is the knowledge of prescribers considering the diagnosis and treatment of CIOP adequate?
5. Could a pharmacy based multifaceted intervention contribute to the improvement of prevention of CIOP?
6. Is a pharmacy based multifaceted intervention effective to reduce actual and potential drug related problems in patients undergoing major orthopedic surgery. Main components of the intervention were medication reconciliation at the preoperative surgery clinic, at hospital admittance and at discharge. Moreover, a clinical medication review was performed by a hospital pharmacist after each reconciliation. Finally, the hospital pharmacist proposed interventions to the anaesthesiologist considering peri-operative drug management.

Part I: Pharmaceutical care in patients at risk of CIOP

International trends in prevention of CIOP

In order to determine which knowledge gaps existed in the field of prevention of CIOP we performed a systematic review (chapter 2). The first studies in the UK (1995[7], 1996[8]) demonstrated that as few as 1% of patients on CS were receiving effective treatments such as bisphosphonates. In order to objectively determine the quality of these observational studies we looked for a measurement tool. For clinical trials these models have been published[9] but no tool could be retrieved for observational studies. Therefore, we developed our own model using the five major criteria present in all referenced guidelines in the studies retrieved. The review showed only 9.4% of the 24 included studies used all 5 major criteria for prophylaxis decision making regarding the in- and exclusion criteria of their patients. This means that in only 9.4% of studies all included patients needed prophylaxis according to the guideline. The results of our review show that study quality was the only significant predictor of the prevention rate determined in the studies. Therefore, the longitudinal increase in prevention rates cannot be attributed to an actual increase in doctor's compliance to the guidelines. It remains unknown whether prevention rates were really as low as studies reported.

The major strength of this study is that for the fist time a model has been developed for the determination of study quality of observational guideline compliance studies in osteoporosis.

The two included intervention studies were multifaceted, the main component being education of general practitioners, pharmacy staff and patients[10] or a small group of specialists[11], respectively. Both studies used a historic control group. Therefore it remains unclear what the real effects of these interventions were.

In our opinion intervention strategies must be multifaceted[12] and directed at educating prescribers of CS, informing patients when prescribing long-term therapy, and regularly informing patients at the moment of dispensing about the effects of CS on bone. We advocate that this can only be effectively done in a regional setting. National and regional health-care structures have to be used to compose a multidisciplinary team of professionals leading the interventions on the local level[13]. Furthermore, prescribers can be logistically supported by pharmacists who make CIOP part of their routine pharmaceutical care program for patients presenting to their pharmacy.

Longitudinal trends of CIOP prophylaxis in The Netherlands.

The study in chapter 3 has described the trends in osteoporosis prevention from 2001-2005 in a group of patients in which Dutch guidelines recommend bisphosphonates be used independent of BMD. We have observed improvements in preventive therapy use in those who fulfil Dutch guidelines. Curtis *et al.* showed that in the USA there has been a gradual increase in BMD testing and osteoporosis prophylaxis prescribing in corticosteroid users, although absolute rates remain low[14].

Supprisingly we have shown gender differences: males are still significantly less likely to receive osteoporosis prophylaxis than females. Furthermore, in contrast to females, males showed no significant improvement from 2001-2005. Other studies have also found that males appear undertreated more than females[14;15]. It is possible that females are given more attention than males because of their postmenopausal bone loss, which men do not experience. Therefore, men have a 20% lifetime risk of fractures, compared to 50% in women[16]. However, the reasons why men are less treated remain enigmatic since ample treatment options are available[17]. Further study is required to investigate these gender differences.

DMARD users were two and a half times more likely to receive bisphosphonate prophylaxis. We speculate that this may be related to the particular doctor specialty. If this is true, our data is in agreement with the paper published by Saag *et al*.[15] who found rheumatologists were 3.5 times more likely to prescribe non-estrogen osteoporosis therapy in long-term corticosteroid users. Therefore, we advocate that intervention studies should be performed in the general population in stead of in a specific patient group with specialised doctors.

There are some limitations to our study that require comment. Firstly, we did not have clinical information on our patient group such as BMD testing or fracture history. However, Dutch guidelines recommended all patients commence bisphosphonate if they are on ≥ 15mg/day prednisolon(equivalents) or are receiving ≥ 7.5 mg/day and are postmenopausal or ≥ 70 years (male) independent of BMD. We were also unable to exclude those patients in whom osteoporosis prevention may be inappropriate, for example, patients suffering from alcoholism, dementia, and serious renal impairment. Lastly, we have obtained data from a specific region (and do not have a control group) in The Netherlands and therefore our results may not be generalisable to the entire Dutch population. However, corticosteroid use in our catchment population (0.5%) was comparable to other population-based studies (0.5-0.9%)[8;18] and our exclusion criteria were negligible. Despite our study's limitations, we believe that postmenopausal corticosteroid users are now being reasonably well treated because bisphosphonate use was 61%. Although it is difficult to define an absolute standard of care, recognising contraindications as well as patient refusal or intolerance, we believe that in our population there is probably scope for further absolute improvement in the use of bisphosphonates of approximately 10-20% in females and 30-40% in males.

Doctors' believes and knowledge on CIOP

The intention of this survey we performed in chapter 4 was to investigate the reasons for the discrepancy between guideline recommendations for CIOP and clinical practice. The study showed that 69% of hypothetical patients were treated according to the guidelines. However, on average, 55% of knowledge questions were answered correctly, with only 16% of doctors answering more than 70% of questions correct. Knowledge on BMD-determination and (relative) contraindications for bisphosphonate treatment were the main problem areas. The lack of knowledge of BMD-determination was confirmed by the hypothetical cases, since the largest percentage of doctors answered incorrectly that a BMD-measurement was necessary.

This study has identified several barriers perceived by GPs in the treatment and prevention of corticosteroid-induced osteoporosis. Remarkably, specialists overall did not identify any barriers. Most striking was the perception by GPs that commencement of preventive therapy was the responsibility of specialists, while GPs often manage repeat prescriptions of corticosteroids. Furthermore it must be noted that not only prescriber barriers but also patient barriers concerning adherence contribute to the low prevention rates of CIOP. The correlation of adherence and fracture rate was determined by Imaz *et al*. in a meta-analysis, showing an increased risk for fracture in patients with low persistence with bisphosphonates (RR=1.46 (95%CI 1.34–1.60 (p<0.001)))[19]. This shows the importance of (pharmacy-led) studies designed to assess the effect of interventions to improve compliance and persistence because data from literature show shortcomings in this field. Polypharmacy was one of the more pronounced barriers in this survey. Doctors are often dealing with patients with complex medical problems requiring multiple medications and may not always consider osteoporosis prevention in corticosteroid users[20].

This survey identified that many doctors were unsure if a patient who was intolerant to one bisphosphonate can be treated with another bisphosphonate. Available data show that previously intolerant patients often accept bisphosphonate therapy upon re-challenge[21]. Switching to another bisphosphonate is a good option as well. In the Netherlands, data show that approximately 20% of patients cease taking alendronate after the dispensing of the first prescription[22]. This might be due to adverse events or inadequate patient education.

Specialists and GPs displayed similar levels of knowledge relating to CIOP with scope for improvement. Similar to previous surveys[23,24], GPs indicated (voluntarily) that more education is required to increase awareness and knowledge of CIOP. However, studies on CIOP, using prescriber education as main intervention tool, have inconsistent results. Only 3 out of 5 studies (60%) showed positive results[10;11;25-27].

Of particular importance, 34% of respondents did not know that the risk of the onset of CIOP was greatest in the first 3-12 months of therapy. In the study by Nielsen *et al.*, only 23% of prescribers would start anti-osteoporotic treatment within 6-months of corticosteroid use[28]. Moreover, only 18% of doctors correctly knew that the BMD cut-off values for treatment of CIOP are ≤-1 or ≤-1.5. The prevalent regional GP and Dutch rheumatologist consensus guideline on corticosteroid induced osteoporosis mentions ≤-1 or - ≤-1.5[29] as the cut-off values. The low percentage of correct answers might also be explained by the fact that the Dutch GP osteoporosis guidelines[30] mention no separate BMD cut-off value for CIOP. These guidelines use a T-score cut-off of ≤-2.5 for treating post-menopausal osteoporosis. The Dutch CBO osteoporosis guideline[31] did mention a T-score cut-off of ≤-2.5 for CIOP, with a note that the fracture threshold might be 1 SD higher. However, in the study by Nielsen *et al.*, only 25% of respondents chose a BMD <1.0 as a treatment threshold[28], which is comparable to our results.

Examining the responses from the case scenarios, doctors were generally less likely to prescribe a bisphosphonate unless a BMD had been performed. This may be because, in the doctor's experience, patients may be unwilling to commence therapy unless a BMD is performed[32;33].

Only 53% of doctors would start preventive treatment in a 45 year old female using 10mg/day with a BMD T-score of -1.8. A previous survey had already shown that for a 65 year old postmenopausal woman using prednisolone (40mg/day tapering to 20mg/day), 80% of doctors would prescribe CIOP prophylaxis, while this was only 25 and 10% in a 45 year old premenopausal female and a 45 year male, respectively[34]. The conclusion is that doctors seem to underestimate the risk of CIOP in younger patients. One of the issues might be that it is not clear whether bisphosphonates should be prescribed in premenopausal women. The benefits might not outweigh the risk of high-dose corticosteroids in this group[35].

There are some limitations to our survey. The study size was limited, which limits generalization and statistical comparison between doctors. Respondents may be those with greater interest and knowledge in the area. As we did not obtain non-responder data, we cannot comment on responder bias. The response rate was 29%, similar to that achieved in other surveys of doctors treatment practices[36] and was considered acceptable considering the length of the questionnaire (8 pages)[37]. For example, a osteoporosis knowledge survey of Werner *et al.* showed a response rate of only 19%[38].

The hypothetical educational cases, while having several limitations, offer a novel approach to identify doctors' behaviour with regards to treatment decisions and some of the possible reasons for under-treatment of CIOP. A strength of our study was that the "correct" answers for the knowledge questions and hypothetical cases were based on the prevalent Dutch guidelines and therefore assess the knowledge a prescriber is expected to have[29-31].

Multifaceted intervention on CIOP by pharmacists

The fact that case-finding strategies can improve patient care for postmenopausal osteoporosis[39] raises the question whether this can be achieved by pharmacists in CIOP patients. The study in Chapter 5 shows that a pharmacy-based multifaceted intervention had limited effect on the prescription of bisphosphonates for the prevention of CIOP. The study complied with the quality criteria (Chapter 2), and was aimed at prescriber education on BMD-determination (Chapter 4), case-finding of patients, especially men (Chapter 3), and at re-recommencement of treatment of patients that had ceased bisphosphonate use (Chapter 4). There was a non-significant increase in bisphosphonate use and any treatment for CIOP, but there was no significant difference with the reference group. The demographic data show a significant difference in length of corticosteroid use. Possibly, the patients in the intervention group were qualified as being more at risk because of longer corticosteroid use. However, this difference was not reflected by a significant difference of prevention rates with the control group before the start of the intervention.

Although we determined lack of effect on a population level, the overview of the responses from the GP's showed that an intervention was made in 22% of patients. After correction for patients no longer qualifying for CIOP prophylaxis (died, relocated, bisphosphonate already (re)started, CS ceased), this was 40%.

Since our study didn't use a randomized trial setting, it remains unclear if the non-significant increase in prevention of CIOP is the result of our intervention. The results of our previous study show an even larger (significant) increase of CIOP prophylaxis, after the publication of the Dutch specialist guideline on osteoporosis and CIOP in 2002[40]. The comparison with the reference group shows a similar increase, suggesting that also in this region efforts were made to implement the updated CIOP guideline. It might even be possible that leakage of the intervention to the control region has occurred, for instance by account managers of the pharmaceutical industry, or doctors and pharmacists or post graduate educational training programs.

Overall, intervention studies for CIOP have shown limited effect[10;11;25-27]. Educational interventions in general show different results. A review of Hammick *et al.* determined that inter-professional education is generally well received by participants and enables practitioners to learn the knowledge and skills necessary for collaborative working. Inter-professional education is less able to positively influence attitudes and perceptions towards others in the service delivery team[41].

A limitation of this study was that the intervention wasn't directly aimed at the patient. The community pharmacist gave advice to the GP, without direct patient oriented education at the moment of dispensing of corticosteroids. The intervention would probably have been more effective if the patient had been involved more directly in the process[42-45]. In 2003 the Institute of Medicine in the US recommended that "all health professionals should be educated to deliver patient-centred care as members of an interdisciplinary team"[46].

A factor that might contribute to the low prevention rate of CIOP after the implementation of the 2005 GP guideline is the general problem of ignoring guideline recommendations. Reasons for non-adherence to guidelines are lack of time to study and absorb the presented material, difficulty changing established personal approaches for managing specific disease states and reluctance to accept a decreased freedom of choice[47;48]. In the perspective of the elaboration likelihood model it can be assumed that professional behaviour of doctors is formed under high elaboration and is therefore more resistant to persuasion[49].

From the results we were unable to determine whether participating GPs had any problems with pharmacists' intervention proposals. The results showed that in only 1.6% of responses, GPs considered CIOP prevention the responsibility of a specialist. In the survey in chapter 4 this was one of the three main barriers mentioned by GPs. Although this might be an attitude-related problem, it doesn't seem to be a great barrier at a population level. More-over in the survey the possible barriers were explicitly mentioned, whereas in the intervention study this was a self-reported barrier.

Team-based care is one approach to address to problem of rising health care costs for chronically ill. Especially this approach can prevent errors or omissions caused by fragmented care delivery[50]. The study of Yuksel showed that a screening program using Qualitative Ultrasound (QUS) for osteoporosis performed by community pharmacists doubled the number of people tested for osteoporosis using DXA[51]. Schouten *et al.* showed that quality improvement collaboratives, in

general, showed positive but limited effects. This was partly caused by the heterogeneity of studies in this systematic review[52]. The authors concluded that: "To understand why quality improvement collaboratives work it is necessary to look into the "black box" of the intervention and to study the determinants of success or failure. A detailed formative evaluation of the projects might provide additional insight into these problems".

The study in chapter 3 showed a marked undertreatment of men compared to women. Therefore, we assessed whether an intervention using computer-assisted decision support could enhance the prevention rates in men. Although the male intervention group showed the largest absolute increase in bisphosphonate use compared to the male reference group and the female groups, there still remained a significant difference between male and females. Male sex was also the principal negative predictor of bisphosphonate use. However, from the GP responses, no reasons could be derived why males were particularly undertreated. Other studies also showed that males were undertreated[14;15]. Primary osteoporosis is also undertreated in men[53]. One of the explanations could be that doctors perceive the risk of osteoporosis in men lower than in women, because men have larger bone[54], and the decrease in bone mineral density is significantly smaller[55], resulting in a lower absolute number of men with fractures[56;57]. Finally, it could be because the cost-effectiveness of CIOP prevention is lower in men compared to women[58].
The major reason for non-effective prophylaxis was due to non-responding GPs, although the overall response rate was very high at 87%. This might be due to lack of time or not acknowledging the risk of osteoporosis. Moreover, in this study, no follow-up education was provided when GPs gave reasons for non-prescription and no suitable alternative had been tried. The results also showed that in 13% of cases a plausible reason for non-prescribing bisphosphonates was mentioned (adverse events, contraindication, problems swallowing, problems with adherence, patients refused therapy, polypharmacy, and no CS use at time of letter to GP). Moreover, the results show that 35% of patients ceased CS, died or moved before the intervention could be performed by the GP. This is likely to at least partially explain the lack of effect at the whole population level. Strong opioid use, as a possible marker of progressive disease, was a significant negative predictor of prevention. This means that for the first time we have insight into the actual reasons for non-prescription in the clinical setting. We estimate the absolute optimal standard of care for the prescription of bisphosphonates for CIOP in the general population is 60-70%. The prevention rate of 55% in the post-intervention group didn't quite meet this goal. Probably, the intravenous use of zoledronic acid is an option for patients with problems with swallowing or adherence[59].
Multivariable regression analysis determined that short-term use (90-360 days) of corticosterioids was associated with low prevention rates of CIOP. Most probably these patients belonged to the 23% of all patients that used CS in between the two selection moments. These patients have not been targeted for intervention, although they qualified for prophylaxis of CIOP and didn't receive

prophylaxis. The process of performing the analyses of the dispensing data from the participating pharmacies was quite labour intensive and was therefore performed only twice during the intervention period.

It remains to be investigated what the results would be if the case-finding were performed on a more regular basis, for instance every 3 months. Theoretically, it would be more effective if the case-finding were performed with every dispensing of a corticosteroid. The only possible draw-back from this setting is alert-fatigue if the specificity of the alert is low. Pharmacists and doctors could become immune to alerts if they are non-specific. It has been shown that 49 to 96% of all drug safety alerts are overruled by prescribers[60]. It has been shown that electronic prompts in dispensing software significantly increase the number of clinically relevant interventions by pharmacists[61]. The advanced decision support software used in this study used guideline cut-off points for inclusion of patients, yielding a high specificity. Although BMD determination using DXA is performed in the majority of fracture patients, case-finding is the advocated method for selection of patients with (high risk of) osteoporosis in the general population. The FRAX-tool with or without BMD for the determination of a 10-year fracture risk can assist in making a decision whether to start treatment[62;63]. Integrating the FRAX-tool in the decision support system might enhance the power of the advice provided to prescribers, resulting in increased acceptation of the intervention-proposals.

Currently, the dispensing software used in Dutch pharmacies is not able to perform real time data-processing for advanced clinical decision support. If this advanced clinical decision support can be incorporated into dispensing software, a nationwide trial can be performed in order to determine the real sensitivity and specificity of the system.

Part II: Pharmaceutical care in patients undergoing orthopedic surgery

Clinical pharmacy services in peri-operative drug management

The study in chapter 6 showed that clinical pharmacy services can have a significant impact on patient safety. The average number of potential DRPs in the control group was 3.6 per patient, despite routine electronic medication surveillance, preoperative screening by an anesthesiologist and internal medicine specialist. In the intervention group the number of potential DRPs has been significantly reduced to 1.5 per patient. Moreover a significant reduction in adverse events (e.g. electrolyte disturbances and supratherapeutic INR's) was determined.

Comparison with other studies

In the study of Hanlon *et al*.[64] in 57% of the prescriptions a potential DRP was determined compared to 24% in our control group. This can be explained by the fact that at the preoperative screening less attention could be given to the indication for and the effectiveness or adverse events of the medication, because of the lack of insight in the medical file of the patient from the GP. If more

information had been available more potential DRPs would have been determined and more interventions would have been possible in the intervention group.

Medication reconciliation by pharmacists during the preadmission period has previously been shown to reduce the need for medication clarification postoperatively[65;66]. Our study results support the recent findings from a randomized controlled trial in Canada, which clearly demonstrated that a pharmacist's involvement in a preadmission clinic significantly reduced postoperative medication discrepancies related to home medications from 40.2% to 20.3% of patients in the control and intervention group, respectively[67]. In the study of Hick *et al.* the participation of a clinical pharmacist in the pre-operative setting of a surgical department led to an increased number of clinically relevant interventions[66]. In this study no specific details were given on the number of interventions in peri-operative drug management. The most important contribution to the process was considered transcribing discharge prescriptions.

Medication reconciliation is not the only tool to enhance medication safety. The clinical pharmacist can provide insight in the impact of continuing or stopping these medications. Moreover, it has been shown that as a result of incomplete drug use profiles, omissions to restart medication and lack of information, many modifications are necessary after discharge from the hospital in the medication use of the patient[68]. The studies by Walker and Kaparinar show that a pharmacy-led discharge service leads to significantly less medication discrepancies[69;70].

The higher number of medications reported by patients in the intervention group is not unexpected since other studies have shown pharmacists often obtain more information than physicians and nurses about patients' medication use when they are admitted to hospital[71;72]. The study by Davis *et al.* showed an average number of chronic drugs used prior to hospitalization by patients aged 60 or more of 4.1, compared to 3.5 and 4.7 in the control and intervention group of our study, respectively[73].

The analysis of medication use of the patients at hospital admittance shows that in only approximately 53% of the prescriptions the information from the GP and the community pharmacy is in accordance with patients' actual use. This is similar to prior outcomes[72]. This is partly caused by inadequate compliance of the patient and partly by inaccurate pharmacy and GP data. This inaccuracy is only partly caused by OTC-drug use from the patients. Additionally, 15% of the prescriptions is started in the period between the preoperative screening by the pharmacy and hospital admittance. This result shows the importance of the intake interview at the day of hospital admittance where attention is given to the medication use of the patient and a structured report is provided to the pharmacy.

The results of the intervention group show that in 24% of the patients an adjustment of the medication was necessary before the patient was admitted to hospital, e.g. ceasing of platelet inhibitors and anticoagulants. Furthermore ceasing or tapering SSRI's, stopping or tapering 'wrong drugs' according to the Beers criteria and starting of PPI because of prevention of NSAID-induced gastropathy are interventions for which the general practitioner of the patient or another specialist needs time to discuss with the patient. Therefore timely involvement of the pharmacy in the process

is essential. The preadmission surgery clinic seems to be the ideal time and place in the process for both patient and anesthesiologist in which the clinical pharmacy services start for this patient group.
In the postoperative phase a drug was restarted in 17% of the patients that had been ceased peri-operatively and was omitted to restart at the time of discharge. This is comparable to other studies[66;74]. Furthermore, a drug was permanently stopped by the pharmacist in 32% of the patients because there was no longer an indication. This is likely to result in a reduction in costs and possibly adverse events. Several studies have demonstrated the positive results of medication reconciliation[69;70;75-80].

The major strength of this study is that all possible aspects of pharmaceutical care for surgical patients have been implemented in the intervention group of this study. A complete follow-up of the patients during the whole process from preadmission clinic to discharge was achieved in both the intervention and control group. In contrast with prior studies not only medication reconciliation, or discharge services have been assessed. Compared to the study of Van den Bemt *et al*. peri-operative drug management advice to the anesthesiologist was not limited to anticoagulant drugs[81]. Moreover, all possible DRPs have been determined based upon the widely used and accepted MAI-criteria[82;83], except quality of directions provided to the patient, practicality of these directions and determination whether the cheapest alternative is used.
The study was too small to show an impact on clinical endpoints or health care utilization such as postoperative complications, blood transfusions and unplanned readmissions. The results showed a significant decrease in adverse drug events and on the length of hospital stay. Whether this was as a result of the intervention at reducing the number of potential DRPs, or is a time trend independent of this study cannot be concluded from our data, although it has been shown in some earlier studies[84]. Similarly the interventions are likely to affect clinical outcomes[2-4;84], although the data is not consistent[70]. Further research in this area should be performed in order to specify the relation between potential DRPs, the MAI-score and clinical outcomes.
No one was blinded to the pharmacist intervention, which could have had an impact on the treating doctors to screen more carefully for DRPs themselves. This so called Hawthorne effect could have influenced the effect of the pharmacists' intervention[85].
Finally, the cost-effectiveness of the activities performed by the pharmacist in this study was not determined. Given that this study suggests that the length of stay in hospital may be reduced because of the pharmacist intervention, future studies should address the economic impact of the intervention.

Implications for future research:

The systematic review on prevention of CIOP (chapter 2) resulted in an audit standard that should be used in all future CIOP prevention studies. These guidelines are:

1. Studies should only determine the degree of prevention using a prevalent guideline at the time of the study as reference.
2. CIOP guidelines generally consist of multiple decision making steps for the clinician to consider in the management of the patient. Thus, in order to determine the degree of prophylaxis according to the guideline of the population at risk, all the risk factors needed to make a clinical decision should be considered.
3. Studies should determine the degree of prevention using treatments mentioned in the prevalent guideline excluding calcium/vitamin D, since calcium and/or vitamin D monotherapy are not considered effective options for the prophylaxis of CIOP in any of the referenced guidelines.
4. Studies should not include patients on monotherapy inhaled CS therapy until further evidence on the risk is available.
5. Studies should also determine what percentage of patients refuse treatment or become non-adherent to therapy. Prescribers cannot be accounted for this lack of prophylaxis.

It should be noted that the same system can be applied to other areas of guideline implementation research. The most important measure would be to use the same factors for decision making mentioned in the guideline which is scope of research and for inclusion or exclusion of patients from the studies.

The study on knowledge of prescribers of diagnosis and treatment of CIOP shows knowledge needs to be improved. In our multifaceted intervention only little attention has been given to educational programs. Moreover, only little is known on the effect of educational programs aimed at improvement of knowledge of patients and self-management of CIOP[42;45;86;87].

The pharmacy based intervention study to improve the prevention of CIOP showed no effect on a population level (Chapter 5). One of the explanations was that patients were missed due to infrequent case-finding, since that was rather labor intensive. It remains to be investigated what the effects are if the decision support system that was used is integrated in the pharmacy software that is used in community pharmacies. This creates the possibility of the continuous determination of risk factors for CIOP (e.g. length of use and average daily dose) with each new prescription.

Furthermore effort should be put into determining the sensitivity and specificity or positive predictive value of the clinical rule used in the decision support system. Adjusting the settings of the calculations used might improve these values, further reducing the labor intensity and improving the number of patients receiving an intervention.

Finally, it should be evaluated whether a pharmacy-based intervention study in corticosteroid users, using the FRAX tool to calculate 10 year risk of fractures with or without BMD [62;63;88] can further improve the decision support tool we have developed.

The study on the effect of a multifaceted pharmacy-based intervention on peri-operative drug management in orthopedic surgery (Chapter 6) showed a significant reduction of the number of actual and potential drug related problems. However, because of a limited study size and low incidence of complications in the control group no data could be provided on clinical outcomes such as morbidity, mortality, readmissions, peri-operative blood loss or bleeding index, etc. Future studies should collect and examine the data of these important parameters.
Furthermore it became clear that there is no standardized, validated audit tool for the determination of appropriateness of the medication in peri-operative care. The MAI-score[82;83;89;90] only accounts for a number of drug related problems encountered in peri-operative drug management. The MAI does not provide a score that can be linked to an actual risk of morbidity or mortality. Studies are needed to adjust and validate this tool for studies on peri-operative drug management.
In the development of a checklist for peri-operative drug management it became clear that evidence for continuation or cessation of certain drug classes during surgery is limited. For instance studies on the effects of ceasing Renin Angiotensin Aldosteron System (RAAS) inhibitors (e.g. enalapril) are scarce[91].

The studies performed in this thesis show the profound role pharmacists can play in enhancing medication safety in patients with musculoskeletal disease. In osteoporosis pharmacists can improve the care of 40% of corticosteroid users at risk of osteoporosis. In orthopedic surgery patients more than 50% of drug related problems could be prevented by a pharmacy-based intervention.

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