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The clinical pharmacist improves pharmacotherapy in hospital patients

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Chapter 11

General discussion and perspectives

General discussion and perspectives

Main findings of this thesis

The aim of this thesis was to describe how the clinical pharmacist can improve pharmacotherapy of hospital patients. We performed studies on three different topics. Firstly, we assessed the clinical value of pharmacist-led medication reviews in two complex patient groups: (pre) dialysis patients and older patients with cancer treated with intravenous chemotherapy. Secondly, we focused on the management of metformin associated lactic acidosis (MALA), a rare but serious adverse effect of a frequently used drug for diabetes mellitus type 2. Finally, we identified several potential new drug binding interactions with sevelamer and polystyrene sulfonate, drugs that are often used by chronic kidney disease (CKD) patients.

Chapter 2 of this thesis describes the evaluation of pharmacist-led medication reviews in pre-dialysis and dialysis patients in clinical practice. A large number of different types of drug related problems (DRPs) were detected. Overall, 80% of the patients had on average three medication discrepancies per patient of which the majority (81%) was acknowledged by the nephrologist. Patient counseling in order to improve adherence and adequate timing of administration was performed in 37% of patients. In addition, medication reviews were conducted resulting in prescription changes in 48% of the patients with nearly two medication changes per patient. Ninety percent of these changes remained implemented on follow-up after at least 1 month. Forty-six percent of the changed prescriptions were identified with the STOPP/START criteria, whereas 54% was based on the clinical pharmacists' expert opinion. The average time investment was 85 minutes per patient for the clinical pharmacist and 15 minutes for the nephrologist. For the latter, the time investment and unclear responsibility for medication management due to multiple prescribers were the main reasons to reject pharmacist interventions.

In chapter 3, pharmacist-led comprehensive medication reviews in older cancer patients using both STOPP/START criteria and pharmacists' expert opinion are described. A prevalence of 78% of potentially inappropriate medications (PIMs) and potentially omitted medications (POMs) was found. Pharmacists' expert opinion in addition to only STOPP/START criteria contributed to 49% of the PIMs and 23% of the POMs. A follow-up action was required in 73% of the PIMs and POMs. The number of medicines and Charlson Comorbidity Index (CCI) score were both associated with at least one PIM and/or POM per patient.

The incidence of metformin associated lactic acidosis (MALA) reported in literature varies widely. In our clinical study (Chapter 4), the incidence was estimated at 47 per 100,000 patient-years, which is 5 to 16 times higher than previously reported. This may

be explained by the use of metformin in the presence of risk factors for lactic acidosis. Remarkably, we found that survivors of MALA had a higher metformin serum concentration than non-survivors, probably because of fewer comorbidities in the survivor group.
Several studies suggest that early recognition of MALA and timely starting the right treatment may reduce morbidity and mortality. However, MALA is difficult to differentiate from sepsis, since clinical symptoms are similar. Therefore, in **chapter 5**, a study is presented to establish clinical parameters for identification of MALA in patients with suspected sepsis induced lactic acidosis in the emergency department. The combined parameters lactate ≥ 8.4 mmol/l and creatinine ≥ 256 umol/l showed a sensitivity of 85% and a specificity of 95% for identifying MALA in suspected sepsis induced lactic acidosis patients in the emergency department. When combined with metformin use the specificity increased to 99%. The multidisciplinary, international EXTRIP Consensus Work Group formulated specific recommendations for starting extracorporeal treatment (ECTR) in metformin poisoning. However, the evidence levels of these criteria were low and their validity in clinical practice was not assessed. **Chapter 6** of this thesis describes the study in which we assessed whether ECTR improved outcome of patients with MALA and the clinical applicability of the EXTRIP-criteria for starting ECTR in metformin poisoning. We found that lactate, creatinine, metformin serum concentrations and vasopressor requirement were significantly higher in the patient group that received ECTR. Blood pH and bicarbonate were significantly lower. Mortality, length of hospital stay and mechanical ventilation requirement were not statistically significantly different between the two groups. Despite these findings, ECTR might be lifesaving in MALA, considering that patients in the ECTR-group were significantly sicker than patients in the non-ECTR-group. In 83% of patients, treatment of MALA was in accordance with the EXTRIP criteria and severity of lactic acidosis and renal impairment were the main indications for initiating ECTR.

Drug binding interactions with sevelamer and polystyrene sulfonate were studied using a combined *in silico, in vitro* and *in vivo* approach.
In **chapter 7**, we present a patient with unexplainable low serum quetiapine concentrations. Our hypothesis, that this was the result of a drug-drug interaction between quetiapine and the binding resins polystyrene sulfonate and sevelamer, was confirmed *in vitro* as well as *in vivo*. The *in vitro* binding assay showed pH-independent absorbance inhibition of quetiapine by polystyrene sulfonate and pH-dependent absorbance inhibition by sevelamer. In the *in vivo* experiment, the time of ingestion of quetiapine, polystyrene sulfonate and sevelamer were separated, whereafter serum quetiapine concentrations rose from a not detectable level to a level well in the therapeutic range.
In an *in silico* study, we identified several candidates for potential binding interactions with sevelamer and polystyrene sulfonate. In a large database we determined frequently

co-dispensed drugs and assessed their potential for binding based on pKa value and charge at gastro-intestinal pH levels (**chapter 8**). Hereby, twenty-eight drugs were selected for further *in vitro* experiments. These subsequent *in vitro* experiments revealed 14 and 23 potentially new binding interactions with sevelamer and polystyrene sulfonate, respectively (**chapter 9**). From these findings, the binding interaction between amitriptyline and polystyrene sulfonate was selected for further investigation *in vivo* in healthy volunteers. This study is described in **chapter 10**. The Cmax and $AUC_{0\text{-}8h}$ of amitriptyline decreased by 75% and 73% respectively when amitriptyline was simultaneously ingested with polystyrene sulfonate compared to intake of amitriptyline alone. As a consequence, we recommend staggered intake of these drugs in daily practice. Further research in CKD patients is needed to establish the optimal time interval between intake for safe and effective use of amitriptyline in combination with polystyrene sulfonate.

Discussion and perspectives

In this last chapter, the results of this thesis will be put into a broader perspective with a specific focus on the role of the clinical pharmacist in relation to the three different topics studied in this thesis (figure 1). The goal of clinical pharmacists is to provide appropriate, effective and safe pharmacotherapy for patients to ensure that the drugs prescribed contribute to the best possible health outcomes. To achieve this goal, clinical pharmacists collaborate with health professionals and patients contributing with their in-depth knowledge of drugs including drug action, dosing, adverse effects and drug interactions.[1,2] In this thesis, we have shown that the clinical pharmacist can improve pharmacotherapy in hospital patients by performing generic, patient oriented activities such as pharmacist-led medication reviews and by performing more specific drug oriented activities as the management of MALA and the management of drug binding interactions with sevelamer and polystyrene sulfonate.

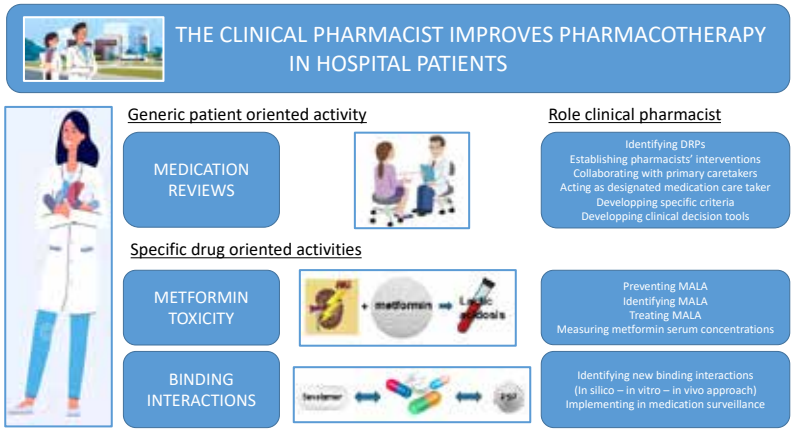

Figure 1 The role of the clinical pharmacist in improving pharmacotherapy of hospital patients; focusing on pharmacist-led medications reviews, management of metformin toxicity and drug binding interactions with sevelamer and polystyrene sulfonate

Medication reviews

We showed that pharmacist-led clinical medication reviews in predialysis/dialysis and older oncology patients with intravenous chemotherapy are good instruments for identifying DRPs and inappropriate prescribing, establishing pharmacists' interventions and improving medication treatment in these patient groups. This is in line with literature.[3-6] There is, however, high heterogeneity in the methods (levels) of performing medication reviews and the reported outcomes.[7] In some studies, patient interviews are not included in performing medication reviews and or only standardized criteria for identifying inappropriate prescribing are used.[8-12] We performed comprehensive pharmacist-led medication reviews including patient interviews and we used the standardized START-STOPP criteria as well as the pharmacists' expert opinion. We showed that half of the PIMs and a quarter of the POMs in older cancer patients were identified by the pharmacists' expert opinion. In addition, in (pre)dialysis patients 46% of the accepted pharmacist interventions was based on the START-STOPP criteria and 54% was identified by pharmacist expert opinion. Strengths of our studies were the combination of pharmacist-led comprehensive medication review and medication reconciliation (described in detail), the incorporation of pharmacists' expert opinion, identifying DRPs, PIMs and POMs and measuring time investment and the follow-up of the recommendations. Both studies were, however, single-center uncontrolled studies and the effects on patient outcomes were not assessed.

Effects on patient outcomes have been studied and published in literature and different systematic reviews and meta-analyses have shown beneficial effects on both medication errors and patient outcomes of conducting medication reviews in hospital patients. Khalil et al. showed consistent evidence of significant reducing both medication errors and medication adverse effects by performing medication reviews in hospital patients but not in preventing death.[7] The systematic review and meta-analysis of Renaudin et al. showed no difference in readmission rates but medication review did significantly lower drug-related readmissions and all cause emergency visits.[13] Another systematic review investigating the effect of medication review in hospital patients on reducing morbidity and mortality showed no significant reduction of mortality or readmission rates.[14] However, there was evidence that medication reviews may reduce emergency department visits. Moreover, Vestergaard et al. showed a significant reduction in the number of readmitted patients within 30 days and within 180 days after discharge by performing extended medication reviews in hospital patients.[15]

Despite these beneficial effects, implementing structural pharmacist-led medication review in hospitals may be too expensive or too difficult to organize.[7] This was also one of

the barriers we encountered in our studies. The time investment in predialysis/dialysis patients was 118 minutes for one accepted pharmacist intervention. Another barrier was unclear responsibility in medication management between different prescribers. This was an important reason for nephrologists to not implement a pharmacists' intervention. In the PIMPOM study we showed that 73% of the PIMs and POMs identified by the pharmacist needed follow up according to the oncologists/hematologists. They delegated 44% of this follow-up to the general practitioner but this was not further evaluated with the general practitioners.

In what way may the clinical pharmacist stimulate medication reviews in hospital patients in clinical practice?

It is essential that primary and secondary caretakers work together in this process. Walraven et al. concluded that medication reviews in hospitals have to be complementary to medication reviews in primary care.[16] Therefore, a medication review in a hospital has to focus on complex patients (chronic polypharmacy patients treated by specialists in the hospital) and on high-risk patients (patients with high risk of medication errors for example at the emergency department). There have to be clear agreements on patient selection, responsibilities and communication between secondary and primary caretakers to improve the process of medication review.[16]

Complex patients

We think the clinical pharmacist can play an important role in improving pharmacotherapy of complex patients, i.e chronic polypharmacy patients treated by specialists in the hospital, acting as designated medication management care taker, making agreements and communicating with secondary as well as primary caretakers. In this thesis, we focused on two groups of complex patients, i.e. (pre)dialysis patients and older patients with cancer treated with intravenous chemotherapy. Other complex patients, which may be interesting for pharmacist-led medication reviews in hospitals are chronic heart failure patients or patients treated by clinical geriatrics. To further improve the efficiency of the process and reducing time investment of medication review, it is important to focus on specific problems in these complex patient groups. We showed that the START-STOPP criteria were not fully suitable in (pre)dialysis patients and therefore the clinical pharmacist may develop specific criteria for performing medication reviews in specific patient groups and implement these into clinical rules in the electronic medication surveillance system of the hospital. Attempts for such a selection algorithm have been done in the primary care setting.[17] This has to be further studied and validated. Additionally, a large part of time spent during the medication reviews consisted of medication reconciliation

activities because electronic medication systems in hospital and in primary care are not identically. Time investment would be drastically reduced if there were a national electronic system with up to date patient medication overviews available used in both primary and secondary care. Hopefully, the current efforts of personal health areas (PGOs) will improve this. Finally, expanding prescribing responsibilities for clinical pharmacists will improve efficiency and reduce time investment of pharmacists-led medication reviews. This is already current practice in other countries as the United Kingdom, the United States of America and New Zealand.[18] In the Netherlands, this has already been regulated by law for specialized nurses and physician assistants, but not for clinical pharmacists. Further evaluation of these suggestions is necessary.

High risk patients

The other group of interest concerns high-risk patients, i.e. patients with a high risk to experience preventable harm from medication. Several studies have been performed to identify high-risk patients in the emergency department for conducting pharmacist-led medication reviews.[19-23] Hohl et al. developed a clinical decision tool to identify patients in the ER with high risk of adverse effects. This clinical decision tool was based on age, the use of opiates/antihypertensives/antibiotics, recent medication changes (last 28 days), number of drugs used (≥ 4 drugs), recent hospital admission (last month) and renal function (creatinine > 150 ug/l). The sensitivity was > 90% and the specificity was 40% when used by clinical pharmacists.[19] Conducting a medication review based on this tool resulted in a reduction of hospital length of stay of 0.48 days in patients < 80 years of age and 0.6 days in patients ≥ 80 years of age.[20] Bonnerup et al. studied the use of MERIS (Medication Risk Score), developed by Saedder et al., in the emergency department clinical practice to identify patients at risk for medication errors.[21,24] MERIS is a score based on renal function, number of drugs and the toxicity and drug-drug interaction potential of drugs involved. Conducting medication reviews in the ER by pharmacists based on MERIS did however not result in reduction of prescribing errors during admission, mortality and health care consumption 90 days after discharge or an improved quality of life.[22]

In a recent systematic review different tools varying in complexity, outcome measures and validation were identified for screening older patients at risk for drug related problems on hospital admission.[25] The BADRI score showed the best results, which is based on number of drugs used (≥ 8 drugs), hyperlipaedimia, increased white blood cell count, use of antidiabetics and length of stay ≥ 12 days).[23,25] However, at present no tool is suitable for clinical implementation yet and more studies on clinically suitable tools to identify high-risk patients in the emergency department are necessary.[25]

In this thesis, we have not studied the effects of medication reviews by a clinical pharmacist in patients at risk for medication errors in the ER. We agree however with Brady et al., that clinical decision tools may be beneficial for identifying patients at risk for medication errors in the ER.[25] For the identified high-risk patients, the clinical pharmacist may conduct medication reviews to assess drug related problems and propose suggestions for optimizing pharmacotherapy during hospital admission. In this way, for example, the rare but serious adverse effect of metformin, MALA, could be identified and managed by a clinical pharmacist at the ER, which is discussed in the next topic.

Metformin toxicity

Management of MALA

The incidence of MALA may increase in the coming years by the release of the contraindication for metformin in patients with more severe renal failure (eGFR < 45 ml/min).[26] Different studies showed the advantages of metformin in CKD patients with a decreased risk of all-cause mortality and ESDR progression without increasing the risk of lactic acidosis.[27,28] When dosages are adjusted to renal function there is no increased risk of lactic acidosis.[29]

Although not withholding metformine from CKD patients seems justified, our studies and literature show that more awareness and attention for the management of lactic acidosis in metformin use is warranted and that the clinical pharmacist may play an important role in this.

Preventing MALA

Metformin is the most inappropriate prescribed drug in CKD patients.[30] Patients using metformin are often not counselled about the risk of lactic acidosis and how to prevent lactic acidosis.[31] Also, MALA is frequently not recognized by professionals in the ER.[32] Community pharmacists and clinical pharmacists in the hospital can play an important role in preventing MALA by performing electronic medication surveillance with clinical rules to identify metformin patients with an eGFR < 60ml/min and adjusting the dose accordingly.[33] Secondly, pharmacists can counsel patients using metformin who are at risk for lactic acidosis, i.e elderly patients using RAAS inhibitors or NSAIDs and CKD patients, in order to stop metformin use in case of dehydration i.e vomiting, diarrhoea and decreased fluid intake, which helps to prevent MALA.[34] Additionally, creating awareness by physicians for this serious adverse effect by education and discussing this topic in pharmacotherapeutic meetings, may contribute in preventing MALA. Finally, conducting medication reviews by pharmacists in primary care can help to prevent evolving MALA.[35]

Identifying MALA

Acute deterioration of kidney function is very difficult to predict and may develop very fast.[36] In the ER, several patients with MALA are admitted every year.[32] It is important to recognize and identify MALA in the ER to start the right treatment. We investigated several criteria to distinguish MALA from sepsis in the ER. A lactate concentration ≥ 8.4 mmol/l and creatinine ≥ 256 umol/l in combination with metformin use appeared to be suitable criteria to identify MALA from sepsis. This was in line with the study results of Schadle et al. who also used renal function, lactate concentration and metformin use to identify MALA which they confirmed by measuring metformin serum concentrations.[37] These criteria are important to add to the clinical decision tools to be developed to identify patients with high risk of medication errors in the ER.[37,38]

Additionally to the above-mentioned criteria, metformin serum concentrations may be an important diagnostic criterium for identifying MALA in the ER. Several studies showed a clear relationship between metformin accumulation and lactic acidosis.[39-41] Bennis et al. showed that metformin concentrations > 9.9 mg/l were associated with lactic acidosis (sensitivity 67% and specificity 93%).[42] In order to use metformine serum concentrations for MALA identification, a 24/7 availability of laboratory facilities is needed. The clinical pharmacist is responsible for these facilities in relation to therapeutic drug monitoring and clinical toxicology of metformine, amongst other drugs and xenobiotics.

Treating MALA

The clinical pharmacist can advise the ER physicians in starting the right treatment in MALA patients. Medication reviews based on clinical decision tools may improve this process. For MALA, ECTR is the treatment of choice.[43] Although we did not measure a significant difference in mortality comparing treatment of MALA with ECTR to treatment with no ECTR, we found that ECTR might be lifesaving considering that patients in the ECTR group were much sicker. Severity of lactic acidosis and renal impairment appeared to be the main criteria for starting ECTR in clinical practice. The EXTRIP-criteria for starting ECTR in metformin toxicity are applicable in MALA and are in line with clinical practice. Bennis et al. suggested to add a metformin concentration > 9.9 mg/l as a threshold for starting ECTR, which makes measuring metformin concentrations even more important.[42] The prognostic value of metformin serum concentrations is however not clear yet. In the study of Bennis et al, metformin concentrations > 9.9 mg/l were not associated with mortality.[42] In addition, in our study, we found no association of metformin concentrations and mortality. Survivors had even higher metformin serum concentration (18.9 mg/l) than non-survivors (2.9 mg/l, p=0.006) which could be explained by less severe underlying disease in patients who survived MALA, rather than an effect of metformin itself. This is in line with literature showing that mortality in lactic

acidosis induced by metformin was lower than lactic acidosis from other causes.[44,45] Metformin may have tissue protective effects but in MALA these effects are probably decreased.[45]

Large prospective randomized trials for management of MALA are difficult to perform because MALA is rare and comorbidities may contribute to lactic acidosis. We think future clinical pharmacist activities should focus on preventing MALA, by performing adequate medication surveillance, counselling patients and creating awareness with physicians as well as developing clinical decision tools to identify MALA in the ER.

Binding interactions

Management of drug binding interactions with sevelamer and polystyrene sulfonate

In silico-, in vitro and in vivo approach

In this thesis, it was unique that we studied drug binding interactions with sevelamer and polystyrene sulfonate by an *in silico-, in vitro- and in vivo* approach. This model offers many opportunities for clinical pharmacists in identifying new drug binding interactions. Clinical pharmacists have access to dispensing data of their patients and have knowledge on chemical properties of drugs. In this way, we identified clinically relevant candidates for potential binding interactions with sevelamer and polystyrene sulfonate for further *in vitro* studies. We have shown that *in vitro* experiments are a relative quick and simple tool to identify many potential novel drug binding interactions. We identified 37 potential new binding interactions with sevelamer and polystyrene sulfonate. The well-described design of the study, mimicking gastro-intestinal environment, makes it easy to reproduce in clinical pharmacy laboratories performing routine Therapeutic Drug Monitoring and Clinical Toxicology assays. This design did not reflect all physiological factors influencing absorbance of drugs. Therefore, confirmatory *in vivo* studies remain necessary to assess the clinical relevance. In literature, there are more sophisticated *in vitro* and computational designs described to study drug binding and drug absorbance that are worthwhile to investigate, because they may reduce necessary confirmatory *in vivo* studies.[46,47] However, these are not available in routine daily practice of clinical pharmacists.

We have shown that *in vitro* binding to sevelamer and to polystyrene sulfonate is well predicted based on pKa values. Clinical pharmacists can use their knowledge of chemical properties as pKa values and analytical assays for quantifying drugs for further executing relevant *in vitro* studies for binding interactions with these resins. Relevant

candidates from our *in silico* study which we have not studied *in vitro* yet are several antihypertensives and antibiotics. This *in silico – in vitro* approach can also be expanded to other resins such as colestyramine and the newer potassiumbinders patiromer and sodiumzirkoniumcyclosilicate. Another chemical property we took into account was the log P value for predicting binding to sevelamer. Log P, however, appears to be less suitable for predicting binding to sevelamer *in vitro*. Walker et al. showed that pKa in combination with log P (= log D) showed the best prediction for binding interactions with colesevalam.[48] Further investigation into the application of these combined parameters is warranted.

When selecting candidates for confirmatory *in vivo* studies it is important to take into account the extent of relative binding *in vitro*, the incidence of concomitant use, the availability of a clinical parameter to evaluate clinical effectiveness, the consequences of therapeutic failure and the needed number of dosages of the drug per day. Based on these factors we suggest further *in vivo* studies for sevelamer with flucloxacillin, acetylic salicylic acid, cotrimoxazole and amiodarone. For polystyrene sulfonate there are many drugs, which probably will bind *in vivo*, but based on above mentioned criteria we suggest to start with amitriptyline, amiodarone, metfomin and cotrimoxazole.
In this thesis, we studied the possible binding between amitriptyline and polystyrene sulfonate *in vivo* in healthy volunteers instead of CKD patients. We assume that binding of drugs in the gastrointestinal tract will be at least as high as in healthy volunteers, since several studies have shown that many CKD patients experience gastroparesis which may lead to even longer contact time of polystyrene sulfonate with amitriptyline.[49,50] The cross-over design with the standardisation of food consumption during intake of medication is a strength of our *in vivo* study because of reduction of variation between subjects and variation of food effects on Cmax and $AUC_{0\text{-}8h}$. Performing *in vivo* studies in patients is far more difficult and has more risks compared to healthy volunteers because of the necessity of introducing wash out periods and changes in clinical dosing regimens. In addition, patients use many more drugs, which can influence the specific binding and take medication with different meals.

Implications for clinical practice

The results of our binding interaction studies are highly relevant for clinical practice. *In vivo* binding interactions that are identified and confirmed have to be implemented in the electronic medication surveillance systems used by pharmacists and physicians with the advice to stagger dosing. The duration of time needed between intake is, however, not clear yet. In practice, a time interval of three hours is recommended, which is based on the time needed for gastric emptying in healthy individuals.[51] Because of the

higher incidence of gastroparesis in CKD patients a longer time interval between intake may be needed for which further research is needed. This also counts for the impact of decreased bioavailability on clinical effectiveness.

In addition to monitoring binding interactions in electronic medication surveillance, it is important to assess binding interactions in medication reviews. When performing medication reviews in patients using sevelamer or polystyrene sulfonate in primary and secondary care it is important for clinical pharmacists to evaluate the ingestion times of the concurrently used drugs and the clinical effectiveness of these drugs. When the effect of a drug taken together with sevelamer or polystyrene sulfonate is low, the clinical pharmacist should analyse if this may be due to a binding interaction. Changing therapy or introducing staggered dosing may be an option to improve treatment of these patients. On the other hand, when patients are well treated with drugs that are ingested simultaneously with sevelamer or polystyrene sulfonate it is important to inform patients to maintain this dosing scheme, because changing ingestion times may result in introducing adverse effects.
Finally, it is important for clinical pharmacists to create awareness with prescribers for these binding interactions and their clinical implications.

Conclusions

This thesis describes different studies of how the clinical pharmacist can improve pharmacotherapy in hospital patients focusing on three different topics: pharmacist-led medication reviews, management of metformin toxicity and management of drug binding interactions with sevelamer and polystyrene sulfonate.

The main conclusions

Pharmacist-led medication reviews are a suitable instrument to identify drug related problems and inappropriate prescribing in (pre)dialysis and older patients with cancer treated with intravenous chemotherapy to improve medication management in these complex hospital patients.

The incidence of MALA is 5 to 16 times higher than reported in literature. When managing lactic acidosis in the emergency department the diagnosis MALA should be considered in patients with a creatinine concentration ≥ 256 umol/l and lactate concentration ≥ 8.4 mmol/l. Severity of lactic acidosis and renal impairment are the main indications for initiating ECTR, that may be lifesaving in treating MALA.

Fourteen potentially new binding interactions with sevelamer and 23 potentially new binding interactions with polystyrene sulfonate were established based on an *in silico* – *in vitro* approach, which have to be confirmed *in vivo* to assess the clinical relevance. One of these binding interactions, amitriptyline with polystyrene sulfonate, is confirmed in healthy volunteers. The exposure of amitriptyline was decreased with 75% when amitriptyline was simultaneously ingested with polystyrene sulfonate compared to intake of amitriptyline alone, necessitating staggered dosing between drugs.

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