The clinical pharmacist improves pharmacotherapy in hospital patients

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DOI:
10.33612/diss.182126573

Chapter 1

General introduction

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Clinical pharmacists are specialized pharmacists providing patient care that ensures the appropriateness, effectiveness, and safety of the patients' medication use and promotes health, wellness, and disease prevention. They work in different health care settings, directly with physicians, other health professionals and patients to ensure that the drugs prescribed contribute to the best possible health outcomes. Clinical pharmacists possess in-depth knowledge of drugs including drug action, dosing, adverse effects and drug interactions that is integrated with relevant understanding of biomedical, pharmaceutical and clinical sciences. To achieve desired therapeutic goals, the clinical pharmacist applies evidence-based therapeutic guidelines and relevant professional principles.[1,2] Furthermore, clinical pharmacists are a primary source of scientifically valid information on advice regarding the safe, appropriate, and cost-effective use of drugs. There are numerous examples in literature how clinical pharmacist researchers generate, disseminate, and apply knowledge that contributes to optimizing drug use, avoiding adverse effects and improving health and quality of life.[3-8]

This thesis describes, in three different parts, how the clinical pharmacist can contribute in improving pharmacotherapy of hospital patients.

1. Medication reviews

Pharmacist-led medication reviews aim to improve patient outcomes by preventing adverse drug events and decreasing healthcare utilization. A medication review is a judgement of the pharmacotherapy by the patient, pharmacist and physician by means of a structured critical evaluation of the medical, pharmaceutical and utilization information. In agreement with the patient and his physician, the pharmacist identifies areas of improvement and suggests a follow-up treatment plan.[9-11] Several studies in community pharmacy show that pharmacists, in a multidisciplinary approach, can play an important role in reducing drug related problems by conducting medication reviews.[5-8] In the Netherlands, as well as in a number of other countries, performing medication reviews in community pharmacy is routine practice.[12] In contrast, medication reviews are uncommonly done in hospital patients.

We investigated the benefits of pharmacist-led medication reviews in clinical practice for two complex patient groups in hospital. In our case, we use the concept of a complex patient group for patients with chronic polypharmacy having a high risk to experience drug related problems and being under treatment of one or more specialists in the hospital: pre-dialysis/ dialysis patients and older patients with cancer receiving intravenous chemotherapy.[13]

Pre-dialysis and dialysis patients have a high risk of drug related problems. They have a high incidence of comorbidities like hypertension, cardiovascular diseases, diabetes mellitus and mineral and bone diseases and as a result, they use on average 10-12 different drugs prescribed by multiple physicians. The frequency of hospitalization is high and almost 20% of the hospital admissions might be directly related to drug related problems.[14] Although there is considerable research showing some evidence for beneficial outcomes of pharmacist-led medication reviews in patients with chronic kidney disease, studies are generally of low methodological quality and included small number of patients. Practical aspects are insufficiently described and evaluated in clinical practice and clinical relevance and follow up of pharmacists' interventions are lacking.[15]

Another complex patient group are older patients with cancer. Ageing, multiple morbidities, and the use of multiple medicines make older patients a high-risk group for drug-related problems. The diagnosis of cancer further increases this risk. Cancer treatment leads to the use of more medicines, multiple involved health care providers, and a higher disease burden. Frequent hospital visits and the associated transfer of information about medication use are additional risk factors for drug related problems, which can lead to compromised cancer management plans.[16] Since future life expectancy is increasing, addressing the appropriateness of medication use in this population will become more important.[17] The Dutch multidisciplinary guideline 'polypharmacy in the elderly' recommends comprehensive medication reviews in patients aged ≥65 years with polypharmacy and having at least one predefined risk factor.[10,11] Oncological diseases are not mentioned as a specific risk factor in this guideline and no Dutch study was found investigating appropriateness of medication and the impact of pharmacist-led comprehensive medication reviews in this population. In addition, studies found in literature addressing the appropriateness of the medication in older patients with cancer have various limitations and methods and results differ highly.[16,18]

2. Metformin toxicity

Metformin is the most commonly prescribed oral antidiabetic drug in non-insulin dependent type 2 diabetes mellitus. Although metformin is considered to be a safe and well-tolerated drug, its use may rarely be complicated by lactic acidosis.[19,20] There appears to be a clear relationship between metformin accumulation and lactic acidosis, although some authors have pointed out that several such patients had other confounding risk factors for lactic acidosis.[20-22]

The incidence of metformin associated lactic acidosis (MALA) reported in studies varies tremendously and may increase in the coming years due to the increase in the number of type 2 diabetes mellitus patients and the use of metformin.[20] Several studies

suggest that early recognition of MALA and timely starting the right treatment may reduce morbidity and mortality.[21-25] However, differentiating between various origins of hyperlactatemia can be very difficult in clinical practice and there is a risk of misclassification. For example, the clinical symptoms of MALA and sepsis are similar, but the treatment is different.[26,27] Clinical parameters that can be used to identify MALA patients in patients with suspected sepsis induced lactic acidosis in the emergency department are therefore warranted. In the treatment of MALA, extracorporeal treatments may be necessary to remove metformin, clear lactate and correct acid-base abnormalities. The Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) formulated specific recommendations for starting extracorporeal treatment in metformin poisoning.[19] However, the evidence levels of these criteria are low and their validity in clinical practice has not been assessed yet.

3. Binding interactions

Resins such as, sevelamer and polystyrene sulfonate, are used for binding phosphate and potassium to treat hyperphosphatemia and hyperkaliemia which can cause serious complications in patients with Chronic Kidney Disease.[28] Because of their binding properties, these resins can also bind other drugs in the gastrointestinal tract, thereby decreasing their bioavailability and clinical effectiveness. This is confirmed in literature for several drugs.[29,30] In the Netherlands, these known binding interactions are included in the electronic medication surveillance systems with the advice for staggered dosing between drugs. This is, however, difficult to accomplish in a patient group using on average 8 different drugs a day. In addition, nephrologists may not be aware of binding interactions of these resins with co-medication and their clinical implications.[29] There are potentially many more drugs binding to Sevelamer or polystyrene sulfonate that are not accounted for in the current medication surveillance systems, leading to ineffective treatment in clinical practice. Therefore, knowledge about new binding interactions with sevelamer and polystyrene sulfonate is relevant for management in clinical practice.

Aim of the thesis

The aim of this thesis is to describe in three different areas how the clinical pharmacist can improve pharmacotherapy in hospital patients. The focus of the thesis is on medication reviews, metformin toxicity and binding interactions.

Part 1: Medication reviews

In chapter 2 we investigated the benefit of pharmacist-led medication reviews in pre-dialysis and dialysis patients by determining the number and type of drug related problems, nephrologist acceptance of pharmacist interventions and time investment.
In chapter 3 we determined the prevalence of Potentially Inappropriate Medications (PIMs) and Potentially Omitted Medications (POMs) in older patients with cancer by performing comprehensive pharmacist-led medication reviews: the PIM POM-study.

Part 2: Metformin toxicity

We estimated the incidence of MALA in type 2 diabetes mellitus patients by means of metformin serum concentration measurements and we investigated the correlation of metformin serum concentration with the clinical outcome of MALA in chapter 4. In chapter 5 we explored clinical parameters to identify patients with MALA in patients with suspected sepsis induced lactic acidosis in the emergency department. Finally, in chapter 6, we assessed whether extracorporeal treatment improves outcome of patients with MALA and we evaluated the clinical applicability of the EXTRIP-criteria for starting extracorporeal treatment in metformin poisoning.

Part 3: Binding interactions

In chapter 7 we describe a case report of a patient with unexplainable low quetiapine concentrations. With an *in vitro* and *in vivo* experiment, we observed a potential drug-drug interaction between quetiapine and sevelamer and quetiapine and polystyrene sulfonate, which were not described in literature before. This case report led to a study in which we explored co-dispensed drug use in patients on sevelamer and or polystyrene sulfonate using an *in silico* approach. We identified potential new binding interactions with Sevelamer and polystyrene sulfonate based on the chemical properties of the most co-dispensed drugs. This study is described in chapter 8. We selected several drugs, that we had identified as potential new drug binding interactions with Sevelamer and polystyrene sulfonate and performed *in vitro* experiments which is presented in chapter 9. Finally, in chapter 10, we investigated the potential binding interaction between amitriptyline and polystyrene sulfonate *in vivo* in healthy volunteers in the BIND-study.

In chapter 11, the general discussion, the main findings are discussed and reviewed in the broader context.

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Part 1

Medication reviews