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Medication optimisation in older adults with cancer

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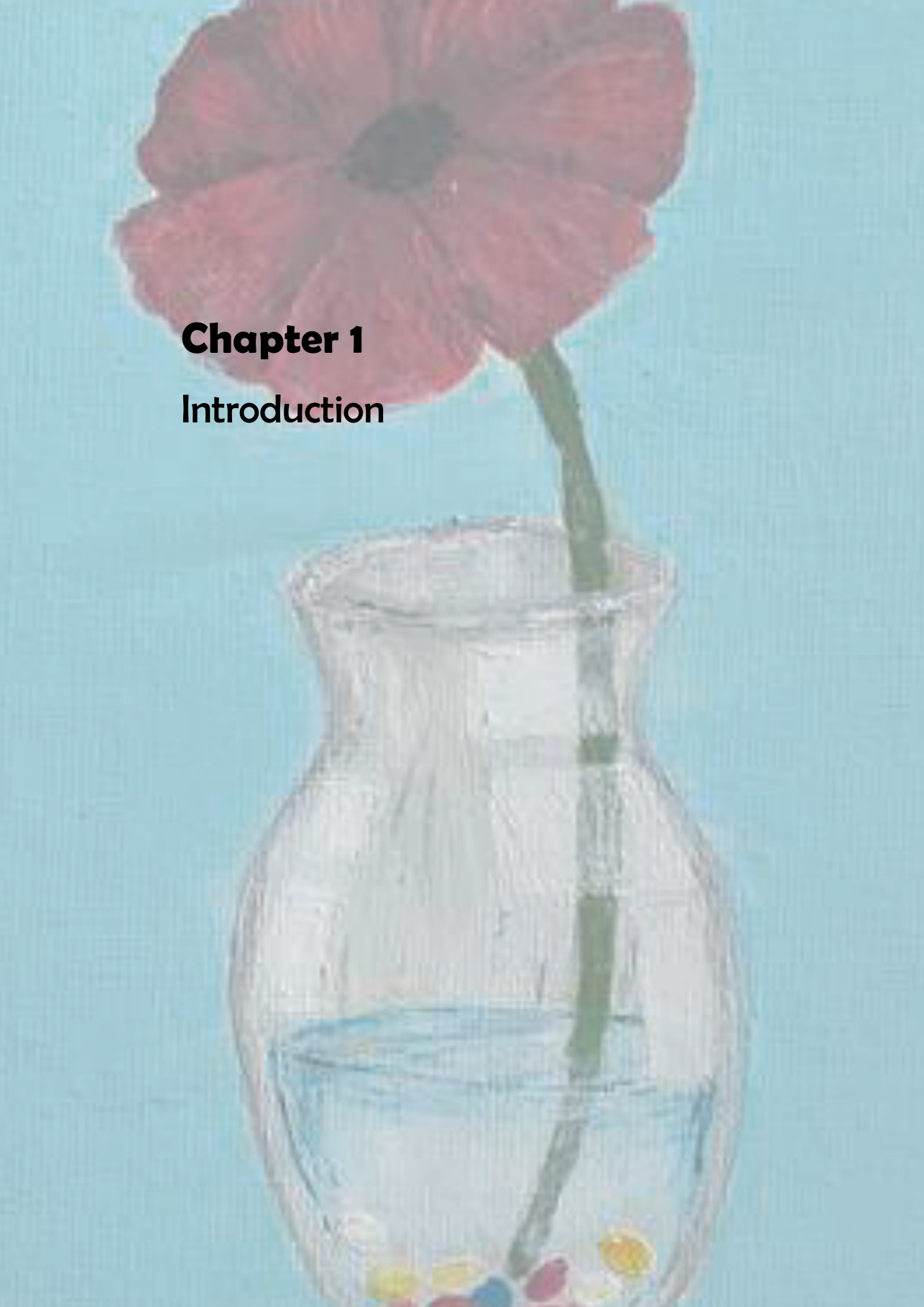
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A painting of a red flower with a dark center, placed in a clear glass vase. The vase is partially filled with water, and the bottom is decorated with several small, colorful pebbles in shades of yellow, red, blue, and white. The background is a solid light blue color.

Chapter 1

Introduction

Introduction

General introduction

Several years ago, as a pharmacist I performed a medication review for Mr Bakker, a 72 year old man with diabetes mellitus type 2 (DM2) and hypertension for which he used 8 different medications, who was recently diagnosed with metastasized small cell lung cancer. Mr Bakker told me he never experienced adverse drug reactions in the past, but recently he suffered from episodes of hypoglycemia and was dizzy when getting up. In the past year, Mr Bakker had lost 15 kgs body weight and due to chemotherapy-induced nausea, his food intake had now decreased substantially. After the second chemotherapy cycle, he had been admitted to the emergency ward with severe hyponatremia. During medication review, a HbA1c of 47 mmol/mol was noted, with 3 daily doses of glibenclamide and metformin and the chart showed low blood pressures with the use of hydrochlorothiazide and losartan. Following discontinuation of glibenclamide, hydrochlorothiazide and losartan, hypoglycemia and orthostatic hypotension markedly decreased. Due to the poor prognosis of Mr Bakker, long-term complications of DM2 and hypertension were no longer a reason for concern and discontinuation of treatment for both conditions could have been discussed at lung cancer diagnosis. Adverse drug reactions with a major negative impact on quality of life would then have been avoided.

Mr Bakker also told me that he took herbal supplements with red coneflower to boost his immune system and red yeast rice to lower cholesterol. He had not told his oncologist about these herbs, nor was he aware that herbal supplements may have interactions with anti-cancer medications. Although scientific evidence on herb-drug interactions with red coneflower is limited and weak, I recommended against its use.

Both the absolute number of older adults that are diagnosed with cancer and the proportion of older adults among patients with new cancer diagnoses is increasing. Many patients are living with frailty and suffer from comorbidities at the time of diagnosis. There is growing awareness that the – frail – older population in oncology practice differs from study populations and more and more research is being conducted on how to predict which patients are at risk for severe treatment-induced toxicity and on how that risk can be decreased. Much less research has been done on the subject of comedications that patients use alongside cancer treatment. Other medications in use may affect cancer treatment, increase susceptibility to adverse drug reactions of both anti-cancer drugs or of the comedication in general, and may decrease quality of life.

Nine out of 10 older adults with cancer have at least one other comorbidity and polypharmacy is common. The use of multiple medications is associated with drug related problems (DRPs), potentially inappropriate medication (PIM) use, and lower quality of life. Especially in frail older patients or patients with limited life expectancy (LLE), the balance between efficacy and safety may become negative due to an increased risk of adverse drug events.

Deprescribing medication is common in of end-of-life care, but it is uncommon in patients with advanced cancer during active cancer therapy. Nevertheless, these patients usually have a limited life expectancy and prevention of long-term health issues may no longer be appropriate. Examples are cardiovascular risk management, the prevention of diabetic complications, or prevention of osteoporosis, yet the corresponding medication use is not re-

evaluated. A plausible explanation is that the focus of oncology teams predominantly is on the treatment of cancer. However, comorbidities and comedications may interfere with goals and outcomes of treatment.

Also, a substantial proportion of patients with cancer use herbal supplements and over-the-counter drugs during cancer treatment, yet frequently do not inform their oncologist about their use. Both herbal supplements and over-the-counter drugs may affect exposure to anti-cancer drugs due to drug-drug or herb-drug interactions. Furthermore, the use of herbal supplements may indicate health issues that a patient experiences, but does not express to their oncologist. Especially the use of herbal supplements and possible herb-drug interactions with anti-cancer medication is a topic of which the relevance in terms of frequency and impact in older adults with cancer is not known.

At this time, pharmacists usually do not take part in the oncological team, yet they are experienced in performing comprehensive medication reviews, including over-the-counter drugs and the assessment of the relevance of drug-drug and herb-drug interactions. Oncology pharmacists usually are more involved in treatment of cancer and not so much in broader care for patients with cancer. In this thesis we will investigate these issues with the purpose of improving the pharmaceutical care for older adults with cancer by the oncology pharmacist.

Scope and relevance of this thesis

The issues addressed in this thesis are not relevant for older adults with cancer exclusively, but may affect younger patients as well. However, as older people in general use more comedications than younger patients and become more susceptible to adverse effects of medications, the issues addressed in this thesis are more pronounced in the older population. All studies were performed in patients aged ≥ 65 years and 1 study included patients aged ≥ 70 years. All patients in our studies received a pharmacological treatment for cancer.

In this thesis, we do not only focus on treatment of cancer, but will address medication-related issues beyond the oncological treatment plan as well. This approach will hopefully increase not only the quality of life of older adults with cancer, but provide practical insights for oncologists and pharmacists who are involved in treating these patients.

Aim

The aim of this thesis is to address medication-related problems in older adults with cancer who receive a systemic anti-cancer therapy. Furthermore, this thesis aims to provide insight in the possible contribution of oncology pharmacists to improve the care for older adults with cancer.

Outline of thesis

Much is known about the anticipated benefits and risks of initiating medications, but information about the discontinuation of medications is lacking, especially in older adults with cancer and a poor prognosis. In Chapter 2, we reviewed the literature about the safety and feasibility of discontinuing chronically used preventive medications in older adults with a limited life expectancy. As extremely little literature is available for cancer patients, we expanded our search to frail older adults and/or people with a limited life expectancy as deprescribing and dose decrease are more common in these patient groups and end-of-life care. We hypothesized that results were applicable to our target population and could support

the recommendations made in the medication optimization intervention described in chapter 2.

Often, older adults use a number of medications for other comorbidities when they start with a cancer treatment. Although they may not be frail, due to a shortened life expectancy a strict treatment of those comorbidities aimed to prevent complications in the future, often is not relevant anymore and even may be harmful. In Chapter 3 we investigated the prevalence of drug related problems (DRPs) and potentially inappropriate medications (PIMs) and the effects of a medication optimization intervention on those problems, as we aimed to decrease the medication burden and DRPs. A medication optimization care pathway was set up for older adults with cancer and a poor prognosis to address DRPs and PIMs, which were assessed by a multidisciplinary team that included a pharmacist.

Fluoropyrimidine-based chemotherapies are a large class of chemotherapeutics that are widely used in the treatment of solid cancers. *DYPD*-guided dosing of the fluoropyrimidine-chemotherapeutics capecitabine and fluorouracil has become standard of care aimed to prevent the occurrence of severe (grade ≥ 3) toxicity. Nevertheless, 23% of older adults still experience severe fluoropyrimidine-induced toxicity. In Chapter 4, we investigated the association of various patient-related variables such as comorbidities, polypharmacy, and BMI with fluoropyrimidine-related toxicity with the goal of supporting treatment-related decisions.

A substantial part of patients with cancer use herbal supplements alongside regular treatment. Often, these patients do not mention the use of herbal supplements to their health-care providers and they may not be aware of potentially harmful effects a herbal supplement can exhibit on the anti-cancer treatment. It is unknown whether supplement use is also frequent among older patients with cancer. Our purpose was to assess the magnitude of the impact of herbal supplements on cancer treatment, which currently largely remains hidden. In Chapter 5 we investigated the prevalence of potentially relevant herb-drug interactions in older adults with a systemic anti-cancer treatment in the setting of a large hospital in the Netherlands.

Older people generally use more medications than younger people, yet they are more susceptible to adverse drug reactions and to anticholinergic side effects in particular. We hypothesized that the anticholinergic burden (ACB) of comedications may negatively impact tolerance and outcomes in older adults who undergo an anti-cancer treatment. We studied the association between a high ACB and severe (grade ≥ 3) toxicity or toxicity-related treatment discontinuation, functional decline or ER-visits and hospitalizations in older patients treated with chemotherapy or targeted therapy. If anticholinergic burden indeed is associated with increased toxicity or the other outcomes, these findings can aid in clinical decision making concerning cancer treatment. The results of this study are described in Chapter 6.

