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## Targeted and Tailored Pharmacist-led Medication Reviews

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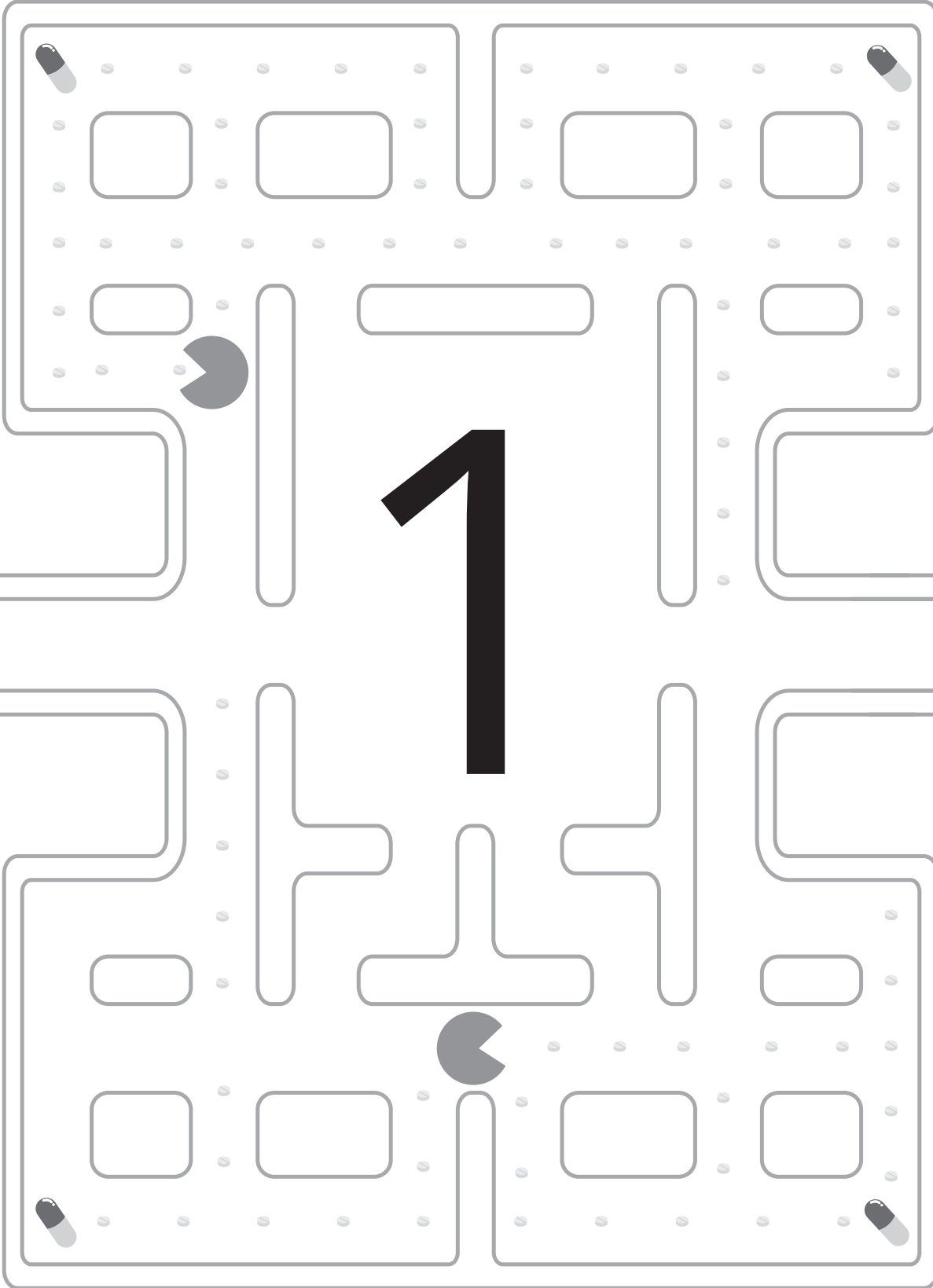
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# CHAPTER 1

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General introduction

## Polypharmacy

In the recent decades the life expectancy in developed countries has greatly increased, in part thanks to modern medicine. This does not necessarily mean that those that live to an old age remain healthy. The number of chronic conditions strongly increases with age. One of the reasons that we are able to live longer with chronic conditions is the widespread use of medication. In 2019 about a quarter of the 1.1 million people between 65 and 74 years of age in the Netherlands used five or more medications for their chronic conditions, and for people above 74 this percentage is almost doubled<sup>1</sup>. In older people the effects of medication are not the same as for younger patients. There are several factors that affect the benefits/risk ratio of medication in this population. In an aging body several pharmacokinetic and -dynamic changes take place that affect how the body responds to medication and how medication is absorbed, distributed, metabolized and excreted by the body. Furthermore, polypharmacy and multimorbidity increase the risk of drug-drug, drug-disease and disease-disease interactions. Polypharmacy -often defined as the use of at least five chronic medications- is associated with a plethora of negative outcomes, such as non-adherence, delirium, frailty, higher mortality and hospitalizations<sup>2,3</sup>.

Cardiovascular disease and type 2 diabetes (T2D) are major contributors to polypharmacy and multimorbidity. In 2019 in the Netherlands about half a million people above 65 years of age used glucose lowering medication and more than two million used at least one medication for cardiovascular disease<sup>4</sup>. Among T2D patients multimorbidity and polypharmacy is the rule rather than the exception<sup>5</sup>. When the disease progresses, polypharmacy is often a consequence as multiple glucose lowering medications might be needed to control glucose levels, statins and antihypertensive medications are often prescribed to lower the risk of micro- and macro-vascular complications and treatment with an angiotensin converting enzyme inhibitor or a angiotensin-receptor blocker is often needed to manage albuminuria. Adverse events caused by cardiometabolic medication, including falls, cognitive decline, hypoglycaemia and muscle pain, can have a large impact on patients' health and wellbeing. Hypoglycaemia is especially dangerous among older T2D patients who have been treated with insulin for a long period of time<sup>6</sup>.

Managing the medication of older people with multimorbidity and polypharmacy is a complex but important task for our current healthcare system. As medication experts, pharmacists can play a pivotal role in this task. Clinical medication reviews have become a valuable tool for community pharmacists to contribute to the medication management of older patients. Pharmacist-led interventions have shown to be effective in reducing inappropriate medication in older people<sup>7,8</sup>.

## Medication reviews

There are many different forms and definitions of medication reviews. The Pharmaceutical Care Network Europe (PCNE) formulated the following definition: “a medication review is a structured evaluation of a patient’s medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug-related problems (DRPs) and recommending interventions”<sup>9</sup>. Medication reviews can be divided into three groups based on the extensiveness of the medication review and based on which information is available to the pharmacist. In simple medication reviews, also referred to as prescription reviews, only medication history is available to the pharmacist. In intermediate medication reviews or compliance/concordance reviews, either additional clinical data or information from a patient’s interview are available. In advanced medication reviews or clinical medication reviews all of the above information is available<sup>9</sup>. In the Netherlands the most common form of medication reviews put into practice in community pharmacies are the clinical medication reviews<sup>10</sup>. A step-wise approach is recommended taking the patient perspective and preferences into account<sup>11</sup>.

Several randomized controlled trials (RCTs) have been conducted to assess the effectiveness of medication reviews but the evidence is still inconclusive<sup>12,13</sup>. This can partly be explained by the diverse approaches for medication reviews, the diverse settings in which they are performed and the diverse goals that are pursued when optimizing medication treatment. Positive effects in meta-analyses are found for reducing the number of medicines, the number of DRPs and the number of falls<sup>12,13</sup>. No effect has been found on mortality and results for the number of hospitalizations are conflicting at bestspaties weghalen tussen best en de referenties<sup>12,13</sup>.

## Patient selection for medication reviews

Clinical medication reviews can be a time consuming and therefore costly process. On average a medication review performed in the Netherlands takes the community pharmacist over 100 minutes to complete<sup>14</sup>. Providing regular clinical medication reviews for all older patients with polypharmacy is near impossible given the rapidly aging Dutch population. It would also result in patients receiving medication reviews who might not need them. In the original Dutch multidisciplinary guideline ‘polypharmacy in the elderly’ published in 2012, the patient selection criteria for medication reviews were being 65 years or older, having five or more chronic prescriptions and having one additional risk factor. The additional risk factors consisted of low adherence, poor kidney function, risk of falls and diminished cognition. However, the information needed to apply these selection criteria was often not available. Without these criteria, it was estimated that more than 1.1 million patients would be eligible for medication reviews based on age and number of chronic prescriptions. Therefore, in the update of the guideline it was suggested to select patients of 75 years or older with ten or

more chronic prescriptions or frail patients<sup>1</sup>. The budget impact analysis showed that these criteria would lead to about half a million eligible patients<sup>15</sup>. Providing medication reviews for this population was estimated to take 1.5 to 4 years and cost 80.000.000 to 100.000.000 euros.

Careful selection of patients who would benefit most from medication reviews is essential to improve the efficiency and to ensure that the conduct of medication reviews remains feasible. Several methods and criteria have been proposed to select patients at higher risk for DRPs and adverse events. Selecting specific subpopulations for a medication review and focusing on specific problems can be a way to make them more efficient<sup>16</sup>. Recently it was concluded that medication reviews targeted at frail, recently discharged, multimorbid patients or patients using antihypertensive or anticoagulant medication have a positive economic effect<sup>16</sup>. Also, medication reviews in diabetes patients showed beneficial effects on adherence and haemoglobin A1c (HbA1c)<sup>16</sup>. A yet to be published subgroup analysis of the DREAMer study showed a larger impact on health related quality of life of clinical medication reviews in patients using more than ten medications<sup>17</sup>. Efforts to develop selection tools for medication reviews have focused on patients who are at high risk for drug related problems (DRPs)<sup>18</sup>. A prioritizing tool based on age, diagnoses and cardiometabolic related clinical measurements resulted in medication reviews with more medication recommendations<sup>19</sup>. Another way to identify patients at high risk for DRPs is the use of patient questionnaires. One study aimed at selecting patients for medication reviews identified five items from a patient questionnaire that correlated with DRPs, which included questions about how often medication instructions were changed, number of doses each day, number of medications, number of diseases and the use of high risk medications<sup>20</sup>. It is not clear whether the use of such questionnaires is feasible and will improve the efficiency of medication reviews. Another study selected patients with a high Drug Burden Index, based on their medication<sup>21</sup>. In this pharmacist-led intervention study, however, the anticholinergic and sedative medication load could not be reduced by the medication reviews<sup>21</sup>. Although a vulnerable population was selected, stopping the psychotropic medication proved to be difficult. These studies illustrate that it is not easy to select the patients that may benefit most from a clinical medication review.

## Deprescribing

Deprescribing inappropriate medication is often part of medication reviews and can be important to combat DRPs and polypharmacy. The term deprescribing was first coined in 2003 in a publication by Woodward<sup>22</sup>. Since then a large variation of definitions have been used in international publications<sup>23</sup>. Although the term deprescribing is sometimes used as a synonym for stopping medication there are some key differences. Deprescribing is a planned process in which a healthcare professional (HCP) stops inappropriate medication in consultation

with the patient to improve patient outcomes and reduce polypharmacy<sup>22,23</sup>. Substituting medication for a less potent alternative or reducing the dose of medication can also be considered as a part of deprescribing<sup>24</sup>. Since deprescribing is a planned process, it can be considered a proactive intervention by a HCP, taking action before adverse effects of medication occur. Identifying adverse effects of medication, is an important aspect of the deprescribing process<sup>22</sup>, reactively stopping of medication can therefore still be considered deprescribing. In deprescribing intervention studies efforts have focused on both reducing polypharmacy and inappropriate medication in general and on specific medication groups which are often high risk and potentially inappropriate in older patients. Examples of medication groups that have been targeted include psychotropic medication, such as antidepressants, hypnotics and antipsychotics, but also preventive medication like bisphosphonates, glucose lowering medication, diuretics and antihypertensive medication<sup>25,26</sup>. Deprescribing approaches, in particular clinical medication reviews aimed at reducing polypharmacy, appear to be feasible, can reduce the number of inappropriate medication and may result in a slight decrease in mortality<sup>26,27</sup>.

### **Deprescribing antihypertensive and lipid lowering medication**

The use of antihypertensive medication in older and frail patients comes with several risks. Antihypertensive medication can cause falls, orthostatic hypotension and/or an imbalance of electrolytes like potassium and sodium<sup>28,29</sup>. Although high blood pressure is an important cause of cognitive decline, low pressure can lead to cognitive decline as well<sup>30</sup>. At the same time there is little evidence for the benefits of long term use of antihypertensive medication in older people<sup>31</sup>. The overall risks of deprescribing antihypertensive medication in older people with relatively low blood pressure levels seem to be small. Available deprescribing trials show no effect on all-cause mortality, stroke and myocardial infarction<sup>28</sup>. A recent non-inferiority RCT in older patients who used at least two antihypertensive medications, mostly for primary prevention, showed that withdrawing one antihypertensive medication resulted in a slight increase in blood pressure<sup>32</sup>. Still, the evidence concerning risks and benefits of deprescribing antihypertensive medication in older people is limited<sup>28</sup>. Available RCTs have short follow-up and are relatively small in size<sup>28</sup>.

Statin use seems to be effective regardless of age, although patients above 75 years of age without occlusive vascular disease seem to have less benefit<sup>33</sup>. The number of studies assessing the effects of deprescribing lipid lowering medication is very limited<sup>25,26,34</sup>. One study evaluated deprescribing statins in patients with a limited life expectancy and concluded that it did not affect survival, increased quality of life and slightly reduced costs<sup>35</sup>.

## Deprescribing glucose lowering medication

The effects of glucose lowering medication in T2D patients on the prevention of long term micro- and macro-vascular complication are well established<sup>36,37</sup>. However, the advantages of tight control reduce with increasing age, number of comorbidities and duration of diabetes<sup>38-41</sup>. Large RCTs showed less benefit of tight glycaemic control in older T2D patient and in the ACCORD trial maintaining a HbA1c below 6.5% was even associated with increased cardiovascular and all-cause mortality<sup>37,40,42</sup>. A longer duration of diabetes or a longer duration of insulin use can increase the risk of adverse effects like hypoglycaemia<sup>6,43</sup>. On top of this, older patients with high clinical complexity based on the presence of dementia, end-stage renal disease or multiple chronic conditions have double the risk of experiencing hypoglycaemia compared to younger less complex patients<sup>44</sup>. For these reasons, national and international guidelines recommend less strict glycaemic control for older and frail patients<sup>45,46</sup>.

Even though it is clear that the benefit/risk ratio of intensive glycaemic control is less advantageous for older T2D patients, especially when insulin is needed to achieve this, evidence about the effects of deprescribing glucose lowering medication is limited. To this date relatively few studies have been conducted and available studies are in general small with a high risk of bias<sup>25</sup>. Still, the available studies indicate that deprescribing glucose lowering medication seems at least feasible and safe<sup>25,47,48</sup>. Deprescribing is possible without large increases in HbA1c and may reduce the risk of hypoglycaemia. Also, simplifications of insulin treatment can result in less hypoglycaemia, without affecting HbA1c levels<sup>49,50</sup>.

## Deprescribing in practice

While overtreatment is common, deprescribing of cardiometabolic medication is still uncommon<sup>25,48,51-55</sup>. HbA1c and blood pressure goals appear not to be tailored based on age, clinical complexity or frailty<sup>25,56,57</sup>. Qualitative research has been done to identify the barriers for implementing deprescribing in general from the HCP perspective as well as the patient perspective<sup>58-66</sup>. HCPs may be reluctant to deprescribe because of a lack of guidelines and evidence about deprescribing<sup>62</sup>. Also, the lack of evidence concerning the benefits and risks of continuing medication in older people complicates decision making. On top of this, adverse events are sometimes difficult to identify in older people with multimorbidity and fear of the negative effects of stopping medication can lead to inertia<sup>62</sup>. General practitioners (GPs) may perceive that patients and their family members are resistant towards stopping medication, and they fear that patients feel given up on when stopping medication is proposed<sup>58-62</sup>. In contrast, about 70 to 90% of older patients reported that they were willing to stop one or more medicines if proposed by their doctor<sup>67-78</sup>. Nevertheless, there are also barriers for patients to stop medication, such as previous bad experiences with stopping, the belief that medication is still needed and not seeing the need to stop medication when they



experience no harm or medication has been used for a long time<sup>58,63-66</sup>. When patients do experience harm or fear harm from their medication deprescribing of becomes more common, for example when patients experience hypoglycaemia due to insulin or sulfonylurea treatment<sup>79-81</sup>.

## Hypoglycaemia

Hypoglycaemia is one of the most important reasons for reducing treatment with insulin and sulfonylureas. It can be defined and subdivided based on blood glucose levels and symptoms. A glucose level below 3.9 mmol/L is often defined as mild hypoglycaemia. In a joint position statement of the American Diabetes Association and the European Association for the study of diabetes, a glucose level below 3.0 mmol/L was proposed as the cut-off point for clinical trials to report hypoglycaemia. A hypoglycaemic event is considered severe when the patient requires help from a third party due to severe cognitive impairment, which tends to occur around glucose levels below 1.5 mmol/L.

Hypoglycaemia is usually associated with strict medication treatment and tight glycaemic control but this is not the only group of T2D patients that are at risk. The HbA1c level has a U-shaped association with both hypoglycaemia rate and overall mortality<sup>82,83</sup>. This implies that patients with high HbA1c levels may also be at risk of hypoglycaemia. With aging and repeatedly experiencing hypoglycaemia, patients can become less aware of hypoglycaemic events because the counter regulation of the body diminishes<sup>84</sup>. This is exemplified by the fact that older patients tend to report less mild events than younger patients<sup>6</sup>. This hypoglycaemia unawareness is an important risk factor for developing severe events.

## Hypoglycaemia rates

Over the past decades, the number of hospitalisations due to hypoglycaemia stayed similar or slightly increased while the number of hospitalisations due to hyperglycaemia steadily decreased<sup>85-87</sup>. The rates of hypoglycaemia among T2D patients differ depending on the medication use of the population and the study methods used<sup>88</sup>. While some studies reported around two events per patient year, others reported close to 40 events per patient year<sup>88</sup>. Of note, in studies with patients using a continuous glucose monitoring system, 75% to 85% of the events were not detected by patients themselves<sup>89,90</sup>. These findings illustrate that hypoglycaemia is far more common than patients report them and thus most likely far more common than their HCPs are aware of.

## Consequences of hypoglycaemia

Hypoglycaemia can have a serious impact on health-related quality of life<sup>91,92</sup>. Patients with hypoglycaemia report less mobility, more pain and discomfort,

more anxiety and depression, and feel more restricted in their activities<sup>91</sup>. Severe hypoglycaemic events have the largest impact on quality of life but frequent non-severe symptomatic events can also result in a decrease in quality of life<sup>92</sup>. Additionally, patients with hypoglycaemia experience fear for hypoglycaemia and more diabetes related distress and they are less productive<sup>93</sup>. Hypoglycaemia can also be a barrier for adequate glycaemic control<sup>94,95</sup>. Concerns about hypoglycaemia can be a reason not to intensify insulin treatment, and fear of hypoglycaemia can reduce adherence to glucose lowering medication<sup>96,97</sup>.

Hypoglycaemia has been associated with increased all-cause and cardiovascular mortality in post-hoc analyses of large trials<sup>98-100</sup>. Hypoglycaemia is known to cause hemodynamic-, electrocardiogram- and coagulation deviations<sup>84,101</sup>. This could explain the increase in cardiovascular mortality, especially in those patients who are already at high risk for cardiovascular events. On the other hand, a recent cohort study concluded that the association between all-cause mortality and hypoglycaemia might be due to shared risk factors<sup>102</sup>.

Hypoglycaemic events result in a substantial financial burden to society. In the Netherlands the costs of hypoglycaemia in T2D patients were estimated to be more than €100 million per year<sup>103</sup>. These costs were largely healthcare related as a consequence of severe events.

## Cause of hypoglycaemia

The cause of hypoglycaemia is multifactorial. Medication use, comorbidities and behaviour can all contribute to the risk of hypoglycaemia. Interactions with co-medication can increase the intrinsic risks of insulin and sulfonylureas. For instance, the use of non-selective beta-blockers can reduce the symptoms of hypoglycaemia, thereby increasing the risk of severe hypoglycaemia due to hypounawareness<sup>104</sup>. Insulin clearance can be diminished due to decreased renal and liver function<sup>104,105</sup>. Depression can lead to poor self-care and self-monitoring<sup>106</sup> and dementia can increase the risk of medication errors<sup>107,108</sup>. Issues with medication taking behaviour, exercise and/or food intake are frequently mentioned as behavioural causes of hypoglycaemia. Dieting, skipped or delayed meals, alcohol use and inconsistent eating patterns can all lead to hypoglycaemia<sup>109-112</sup>. Exercising more or more vigorously than usual and mistakes in the timing and dosing of insulin (for instance accidentally injecting twice) can also lead to hypoglycaemia<sup>109-112</sup>. These behavioural factors that can be a direct cause of hypoglycaemic events highlight the importance of proper self-care and self-management for patients at risk of hypoglycaemia. Self-management of a chronic disease includes the ability to manage the disease with the goal of reducing the negative impact on physical and psychosocial wellbeing<sup>113</sup>. Self-management education for T2D patients has mostly been focused on achieving glycaemic control and reducing cardiovascular risk<sup>114</sup>. Relatively little attention has been paid to self-management problems that can lead to hypoglycaemia in T2D patients.

## Outline

The management of medication treatment in older people with polypharmacy and multimorbidity is a complex yet essential task for our healthcare system. Medication reviews can be a valuable tool for pharmacists to reduce DRPs in this population. Better and more efficient ways to select patients, i.e. a targeted approach for medication reviews are needed in order to 1) reach patients who benefit the most from medication reviews, and 2) make the conduct of medication reviews for those who need it sustainable. Furthermore, to increase deprescribing and to better support older patients using multiple cardiometabolic medications, a more tailored approach may be needed. Both reactive and proactive deprescribing of such preventive medications is warranted when potential benefits no longer outweigh the potential harms. This is particularly the case for older T2D patients who experience hypoglycaemic events or are at high risk for hypoglycaemia. Also, self-management problems related to these events should be identified and addressed.

To develop a new approach for a targeted and tailored medication review, a series of studies were conducted, which are presented in this thesis. In the first part of this thesis, selection criteria for medication reviews are developed to identify (1) older patients most in need of a clinical medication review, and (2) patients at high risk of hypoglycaemia in need of a tailored medication review. In the second part the perspectives of patients on hypoglycaemia and the patients' and HCPs' perspectives on deprescribing cardiometabolic medication are explored. This is done with the aim to identify barriers and enablers for deprescribing and to identify self-management problems related to hypoglycaemia. The results of these studies are then used to inform the design of a targeted and tailored medication review focusing on deprescribing and reducing the risk hypoglycaemia in T2D patients. In the third and last part of this thesis, the feasibility and potential effects of this novel pharmacist-led intervention are evaluated.

### **Patient selection for medication reviews (Chapter 2 & 3)**

In **chapter 2** expert opinion in combination with a Delphi-method is used to develop an easy to apply algorithm with the goal of differentiating between complex and less complex older patients for clinical medication reviews. A pilot in four community pharmacies was performed to investigate the feasibility of the newly developed method to select patients for such reviews. In **chapter 3** a screening algorithm to identify T2D patients at high risk for hypoglycaemia was developed. Several machine learning techniques were tested on data from the GIANTT database ([www.GIANTT.nl](http://www.GIANTT.nl)) in order to develop an algorithm that could be applied on information routinely available in the Dutch community pharmacies.

### **Patients' and healthcare professionals perspectives on deprescribing and hypoglycaemia (Chapter 4-7)**

In **chapter 4** T2D patients' views on causes of hypoglycaemia and underlying self-management problems are explored with a mixed-methods study design combining qualitative and quantitative methods. In **chapter 5 and 6** patients' attitudes towards deprescribing of cardiometabolic medication are investigated, in a qualitative and a quantitative study. In **chapter 7** the attitudes towards deprescribing cardiometabolic medication of different types of HCPs involved in the medication use of older patients are explored in a qualitative study.

### **Feasibility of a targeted and tailored medication review for type 2 diabetes patients (Chapter 8 & 9)**

Based on the results of the previous studies, a novel intervention was developed, which was targeted at T2D patients with a high risk of hypoglycaemia and tailored with the goal of reducing overtreatment with cardiometabolic medication and reducing the risk of hypoglycaemia. In **chapter 8** the potential effectiveness of this intervention is tested in fourteen community pharmacies across the Netherlands. In parallel a process evaluation of this intervention was performed, which is described in **chapter 9**.

The thesis concludes with a general discussion in **chapter 10**.

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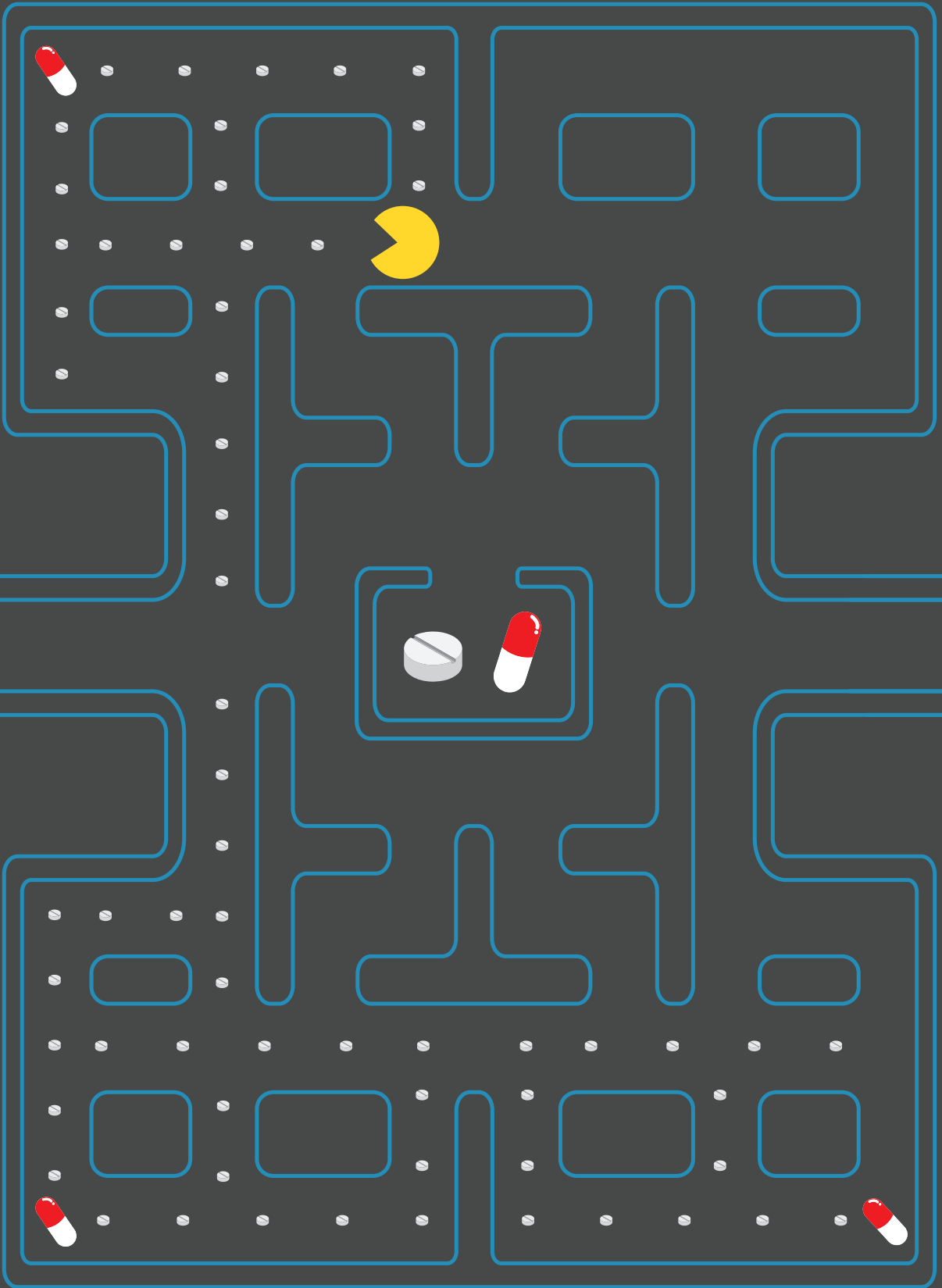
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# PART I

Patient selection for medication reviews