Multidose drug dispensing

for older patients in primary care

Bram J. Mertens

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For reasons of consistency within this thesis, some terms have been standardised throughout the text, As a consequence the text may differ in this respect from the articles that have been published.

Multidose drug dispensing

for older patients in primary care

Medicatie op rol

voor oudere patiënten in de eerstelijnsgezondheidszorg

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
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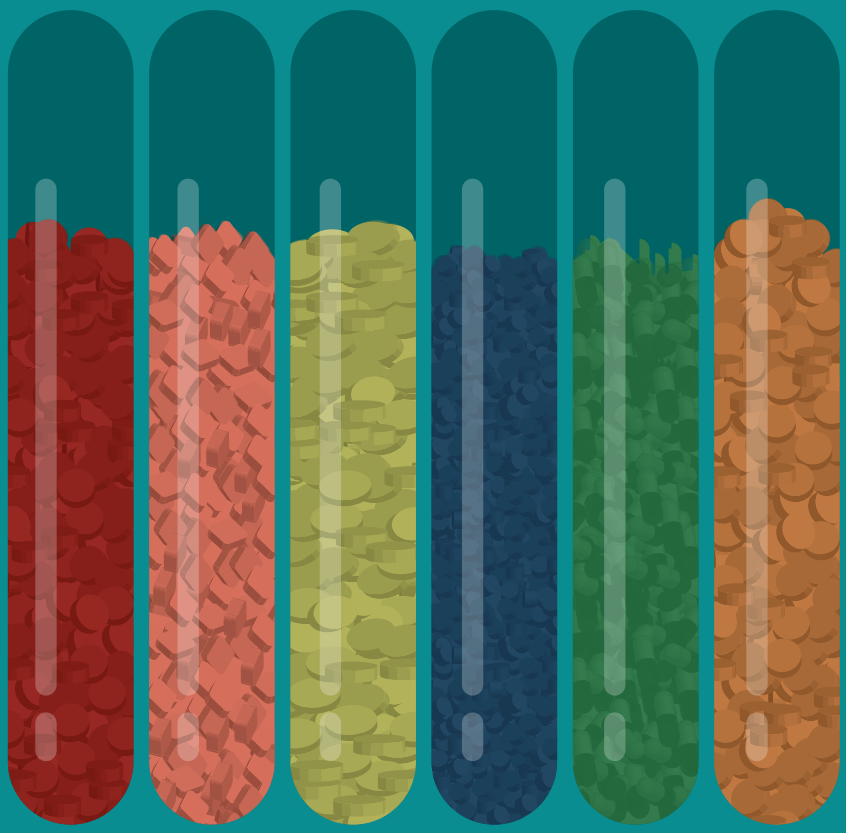

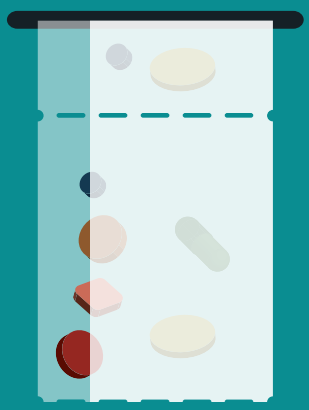

Chapter 1

Introduction

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INTRODUCTION

Older adults are stimulated to live independently in the community for as long as possible.[1] Despite the ageing of the Dutch population, the number of beds in nursing homes is decreasing while the number of community-dwelling older adults is increasing.[1,2] Due to multimorbidity and improved medical treatment options, these patients use an increasing number of drugs, which results in more complicated dosing regimens.[3,4] Over time, the health status of these patients is expected to decline.[4] The decline of a patient's health status combined with the more complicated dosing regimens can result in the loss of the patient's medication management capacity (MMC).[5] Pharmacists have the opportunity to support patients by a wide variety of interventions, but for an intervention to be effective, it must be tailored to the patient's needs.[6-8] One proposed approach for patients with a reduced MMC is the use of dosing aids, especially among patients with polypharmacy or complex dosing regimens.[9-11] Dosing aids are available in various forms, such as pill-boxes, multicompartment compliance aids (MCAs) or automated multidose drug dispensing (MDD) systems (Figure 1). All have their advantages and disadvantages.[12,13] This thesis concerns the use of MDD systems.

FIGURE 1: Examples of dosing aids. (A) pill box, (B) multicompartment compliance aid, (C) multidose drug dispensing system.

Medication management capacity

The patient's MMC is a concept that covers multiple domains.[14] Functional problems, organisational problems, limited medication knowledge, and medication non-adherence all interact and will eventually result in the patient's MMC (Figure 2). Several screening tools have been developed to assess patients' MMC.[15-19]

Functional problems

Older patients frequently encounter problems with medication packaging.[20-22] These functional problems may hamper the appropriate use of their medication. A common cause is impaired dexterity.[21] For instance, rheumatic patients or unilaterally paralysed

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patients often experience difficulties with using manually dispensed medication. The inability to read or interpret information can also hamper the appropriate use of medication, as if a patient cannot read the instructions on drug labels, it is unlikely that the patient will adhere to the instruction. Finally, almost half of all patients have low health literacy, which is correlated with a poor understanding of drug labels.[23]

Organisational problems

In addition to functional problems, organisational problems can adversely affect the appropriate use of a patient's medication. If a patient is disorganised, he might forget to order his medication in time. Organisational problems can evolve gradually or occur suddenly (e.g., when a patient's partner dies or after an event with a strong impact on a patient's health status, such as a stroke or delirium). Another example is that of frequent 'drug label switches', an increasingly prevalent problem caused by the policy of Dutch health insurance companies to preferentially reimburse specific generic brands. Another cause of drug label switches is the increasing number of drug shortages.[24] Drug switches can be confusing, especially for older patients, and this may negatively affect the patient's medication adherence.[25,26]

Medication knowledge

Patients who are unable to identify the appropriate medication package are unlikely to be adherent to their medication regimens. Medication knowledge is therefore an important aspect of the patients' MMC. A low medication knowledge in users of MDD systems was demonstrated in a cross-sectional study by Kwint et al., in which only 40% of the MDD users had adequate medication knowledge.[27] However, it cannot be concluded that the use of MDD systems is the cause of the low medication knowledge. As mentioned, problems in different domains are likely to be correlated with each other. For instance, a patient who is unable to read or interpret information is likely to have low medication knowledge.

Medication adherence

The final aspect of the patients' MMC is medication adherence. It can be argued that medication non-adherence is a consequence of the perceived problems in the other aforementioned domains, but a patient can also be non-adherent without experiencing any problem in the other domains. The more complex a medication regimen is, the more likely it is that a patient will be non-adherent.[28,29] In the previously mentioned study of Kwint et al., current users of MDD systems had higher self-reported medication adherence than that of users of manually dispensed medication.[27]

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The impact of medication non-adherence is significant and associated with decreased health outcomes and increased medical costs.[30,31] To choose the appropriate intervention for a patient, it is important to distinguish between the different types of medication non-adherence; it can be intentional or unintentional, and both can also exist concurrently.[32,33] Intentionally non-adherent patients consciously decide not to adhere to their medication regimens. A wide variety of underlying mechanisms for intentional non-adherence have been identified, but almost all can be related to the patient's beliefs about the disease, prescribed medication or costs.[33,34] Unintentionally non-adherent patients are willing to adhere, but fail. This can also be caused by a wide variety of problems, but generally has a more practical cause (e.g., complex medication regimens, impaired dexterity, and decreased cognition). Often, several causes are present at the same time. Intentional non-adherence is best targeted with interventions focused on the patient's beliefs with regard to his illness or medication.[33] Unintentional non-adherence is best targeted with a more pragmatic approach that is focused on the causes.

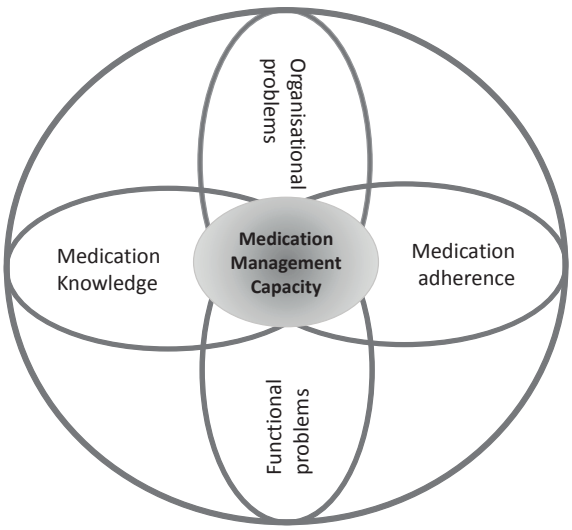

FIGURE 2: Schematic presentation of patients' medication management capacity.

Multidose drug dispensing (MDD) systems

In the Netherlands, medication is dispensed by the community pharmacist, either in the original packaging (manual dispensing), or via a dosing aid, of which MDD systems are the most commonly used type. In an MDD system, the patient's medication is removed

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from its original packaging and automatically packed in disposable plastic pouches (Figure 1). These pouches are labelled with patient data, the date, the time of intake, and the pouches' contents.[27] MDD systems are available in different forms but multidose is mainly used. In multidose, all medication from one dosing moment is packed in a single pouch.[12,13] Not all medication can be dispensed via an MDD system; in general, only capsules and tablets with a fixed intake schedule for oral use are packed. For instance, sachets, inhalers or suppositories cannot be dispensed via an MDD system.

The production of MDD systems requires specialised machinery and specific knowledge. The Dutch and European guidelines for the production of dosing aids have a high quality standard to which community pharmacists cannot easily comply.[12,13,35] As a consequence, most community pharmacies have outsourced dosing aid production to specialised MDD suppliers.[13] In order to produce MDD systems, community pharmacies electronically send the prescription files to the MDD supplier.[27] After filling the MDD systems, an automated check on accuracy, using photographic techniques, is performed. The actual content of each sachet is compared with their theoretical content based on the prescription files. Potential inequalities identified by the automated technique are visually checked by trained staff. Confirmed inequalities are corrected and visually double-checked.[12,35] After completion, the MDD systems are sent to the community pharmacy, which dispenses the MDD system to the patients. Because the medication is stripped from its original packaging, light, air, heat and humidity can affect the quality of the medication.[12,36,37] MDD systems are dispensed only for a short period of time (one week, two weeks or three weeks) to minimise these effects.

The use of MDD systems in the Netherlands

MDD systems were first introduced in the Netherlands in the mid-1990s. Prior to this, MCAs that were manually filled by pharmacy technicians were used. With the introduction of the MDD system, dispensing medication via dosing aids became less labour-intensive and resulted in a reduction in the number of administration errors in nursing homes.[38] These advantages combined with the reimbursement by the health insurance companies for an MDD system led to an increase in the use of MDD systems. The use of an MDD system must be authorised by a prescriber in order to be reimbursed by the patient's health insurance company. In general, pharmacists receive the costs of the dispensed medication and a dispensing fee. As a result of the high dispensing frequency of MDD systems, the dispensing costs via an MDD system are approximately €100 higher per dispensed drug per year compared to manually dispensed drugs.

Currently, MDD systems are widely accepted and embedded in daily practice. This is also demonstrated in the number of patients who receive their medication via an MDD

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system, which rose from around 400,000 in 2014 to approximately 500,000 (3% of the Dutch population) in 2017.[39,40] The large-scale use of MDD systems in primary care is limited in other countries. As far as we know, it has only been implemented on a large scale in the Netherlands, Scandinavian countries and Australia.

Users of MDD systems can be roughly divided into three categories. The first and largest group of patients is the community-dwelling older adult with polypharmacy.[13] MDD systems are used to structure the patients' complex medication regimens in an attempt to improve their medication management. The second type is the complex psychiatric patient. These patients are often disorganised because of their psychiatric disorders. In addition to an attempt to improve their medication management, dispensing medication for a limited period of time prevents medication abuse in these patients. The third group of patients receive professional home care or live in nursing homes. These patients are supported by professional care workers who are responsible for the patients' medication administration. Dutch legislation requires that these patients receive their medication in dosing aids to minimise the risk of administration errors.[41]

What is known about the quality of drug treatment of MDD users?

In various studies, the use of dosing aids has been associated with low-quality of drug treatment.[42-47] The quality of drug treatment can be reflected by the prevalence of potentially inappropriate medications (PIMs). PIMs, especially for older patients, are defined as medications for which the potential risk outweighs the potential benefit, or that are ineffective (e.g., psychotropic drugs, long acting benzodiazepines, anticholinergic drugs). One study showed that after the initiation of MDD systems, patients used more drugs and more PIMs.[46] In a different study, fewer medication changes were implemented after a hospital admission due to a hip fracture among users of MDD systems compared to users of manually dispensed drugs.[42] It has been suggested that fewer drug changes are caused by the automatically repetitive process of distributing medication via MDD systems. Most studies have been conducted in Scandinavian countries, and have a cross-sectional design without a comparable control group. Users of MDD systems are generally older patients who use a high number of medications. Therefore, more longitudinal studies with matched control groups are warranted.

What are the patients' experiences with dosing aids?

Dosing aids are used to support patients with their medication use. To optimally support these patients, their experiences with MDD systems must be known. However, the patients' experiences in this regard have rarely been studied. The experiences of Swedish MDD users have been studied most extensively in a survey of 1,465 users.[48]

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The vast majority of users were very satisfied with the MDD system and indicated that the MDD system indeed supported their medication use. Divergent results were found in an English qualitative study of users of MCAs.[49] Some patients were satisfied with the provision of an MCA, as it made them more independent and autonomous, and without an MCA, their daily medication management was too much of a concern. However, some patients felt patronised, as the MCA undermined their autonomy. In both studies, the provision of manually dispensed medication separate from the dosing aid and difficulties in opening the dosing aid were addressed as disadvantages. Based on these results, several guidelines for patients with a dosing aid recommend to stimulate the patient's autonomy. If appropriate, the patient should remain responsible for his own medication.[11-13] In order to achieve this, simple interventions may be implemented, such as electronic repeat dispensing services, the provision of an intake schedule, simplification of complex medication regimens or the use of a pill box that can be filled by the patient himself or an informal caregiver.[50] As patients' experiences have not been studied in the Netherlands, it is unknown whether Dutch MDD users are satisfied with the system, as in Sweden, or have divergent opinions about it, like in England.

What is known about dispensing errors?

Compared to manually filled dosing aids, the use of MDD systems is likely to reduce the number of dispensing errors. In 1992 and 1994, two studies compared the accuracy of automatically filled dosing aids with manually filled dosing aids.[51,52] In both studies, the accuracy was higher in the automatically filled dosing aids than in the manually filled dosing aids. In the automatically filled dosing aids, an accuracy of 99.98% was achieved versus 92.62% in the manually filled dosing aids.[51] Since the 1990s', packaging machines have been improved and their accuracy further increased. In a Dutch retrospective analysis of all reported and documented dispensing errors in 2004, an accuracy of 99.999% was achieved.[53] With the introduction of automated photographic control of the packed medication, the accuracy can be expected to have improved even further.

A significant disadvantage of MDD systems is their rigidity during drug regimen changes. Adjustment of the patient's pharmacotherapy is preferably deferred until the start of the new MDD system.[11-13] When it is inappropriate to defer a medication change, the MDD system must be manually adjusted by the pharmacy; pouches are opened and the adjusted medication is added or removed and the pouch is closed again. Manual adjustment is therefore considered to be a high risk that may lead to dispensing errors. Research is needed to gain insight into how adjustments are effectuated (manually or deferred) by pharmacy staff.

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What is the effect of MDD systems on health outcomes?

The underlying assumption for the widespread use of dosing aids is that an improvement in patients' medication adherence will affect patients' health outcomes.[9,10,13,54] However, whether MDD systems actually improves health outcomes is uncertain. No studies have been conducted with dosing aids that used clinical outcome measures, such as medication-related hospital admissions, morbidity, mortality or health-related quality of life as primary outcomes. Only the effect of dosing aids on intermediate outcomes (e.g., medication adherence, HbA1c, LDL cholesterol and blood pressure) has been studied. In 2011, a Cochrane meta-analysis identified 12 studies that applied dosing aids as intervention.[9] Studies with dosing aids as part of a multicomponent intervention were not included. Two studies assessed the effect of a dosing aid on the patient's blood pressure; dosing aids had an effect on the diastolic blood pressure (-5.9 mmHg) but not on the systolic blood pressure. Two studies used glycated haemoglobin as outcome; a significant decrease in patients' HbA1c (-0.7% mmol/mol) was found.[9] Six studies determined the effect of dosing aids on medication adherence; the use of dosing aids improved the patient's medication adherence by 11%.[9] Two studies that measured self-reported adherence showed no effect from the intervention. The included studies were heterogeneous and had a high risk of bias, which hampered a valid conclusion. None of the included studies used an MDD system as a dosing aid. We identified only one observational Dutch study that studied the adherence among MDD users.[27] In this cross-sectional study among Dutch MDD users, the self-reported medication adherence was measured by the Medication Adherence Report Scale (MARS). Current users of an MDD system reported a higher adherence (81%) compared to patients who received manually dispensed medication (58%). In contrast with the improved adherence, the patients' medication knowledge was lower than that of users of manually dispensed medication (40% versus 79%).

In conclusion, the available evidence on the effects of dosing aids on health outcomes is limited. An improvement in medication adherence and other intermediate outcomes is likely, but the effects on clinical outcomes are unknown. Existing studies applied different type of dosing aids, but the effect of an MDD system has not been evaluated in a randomised controlled trial (RCT).

Objective of the thesis

In summary, due to the ageing of the Dutch population and the government's policy to stimulate patients to continue to live independently in the community, the use of MDD systems is expected to continue to increase. Relative to the large number of MDD users, the effects of MDD systems have been inadequately studied. More knowledge about

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MDD users and the potential effects, advantages and disadvantages of MDD systems is needed. The objective of this thesis is therefore to address the following research questions:

1. Which patients should be selected for the use of an MDD system?
2. How should the pharmaceutical care around MDD patients be optimised?
3. What are the effects of an MDD system on different outcomes?

Thesis outline

The studies described in this thesis are divided into two parts. In the first part, the influence of MDD systems on daily practice is described from different perspectives. In **Chapter 2,** a case-control study is described in which the experienced medication management problems of patients who were about to start using an MDD system were systematically documented and compared to control patients. This is followed by a study on the effect of an MDD system's initiation on the number of drugs and prevalence of PIMs **(Chapter 3)**. **Chapter 4** describes a survey that was conducted to explore the patients' experiences with the initiation and use of MDD systems. **Chapter 5** concerns a cross-sectional study in which was examined how different community pharmacists effectuated medication changes in patients' drug regimens.

In the second part of the thesis, the effect of the initiation of an MDD system on a health outcome is assessed. **Chapter 6** describes the design and rationale of an RCT that assessed the effect of dispensing vitamin K antagonist via an MDD system on the patient's time in therapeutic range (TTR). The effects on the patient's TTR are presented in **Chapter 7. Chapter 8** is an explorative subgroup analysis in which insight is gained into which patients benefitted most in the RCT.

Finally, the results are summarised, discussed and framed in a broader context with regard to the integrated care of patients with an MDD system **(Chapter 9)**.

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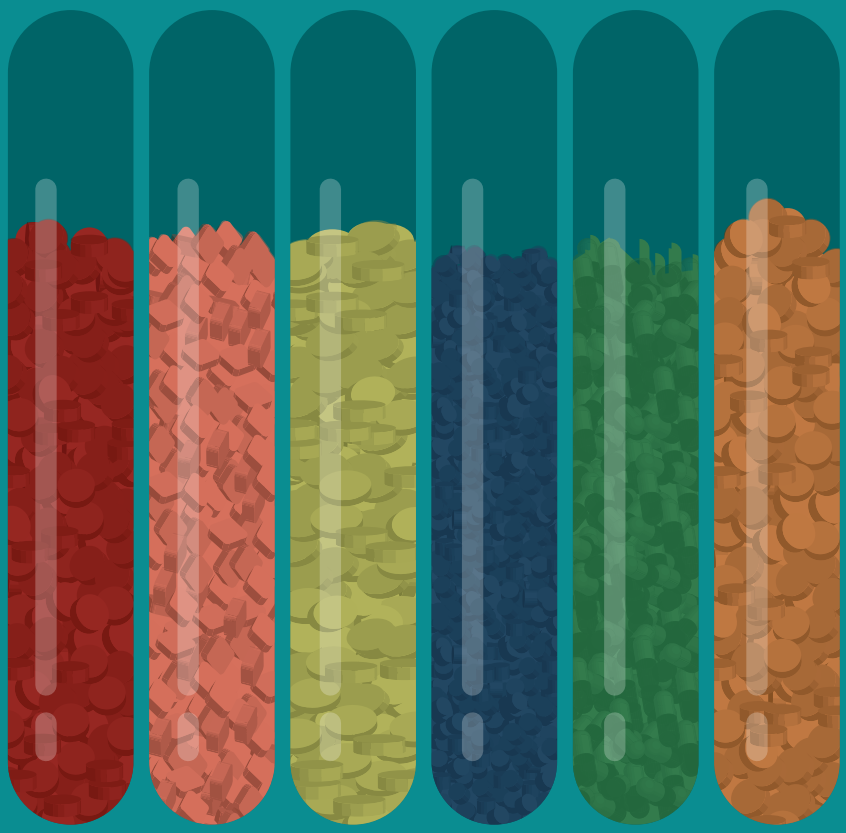

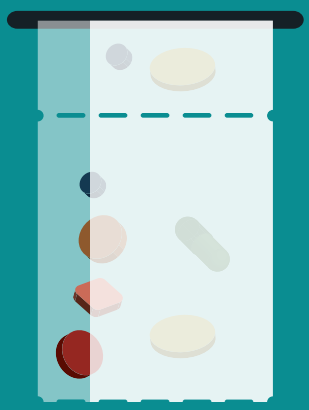

Chapter 2

Are multidose drug dispensing systems initiated for the appropriate patients?

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Abstract

Purpose: It is unknown if automated multidose drug dispensing (MDD) systems are initiated for the appropriate patients. Therefore, the objective of this study was to compare the medication management problems of patients who were about to start with an MDD system (MDD patients) and patients who continued manually dispensed medication (non-MDD users) in order to identify if the appropriate patients receive an MDD system.

Methods: Patient interviews (semi-structured) were conducted by 44 community pharmacists at the patient's home. Patients over 65 years of age, home-dwelling and using at least 5 chronic drugs were eligible for the study. An assessment tool was developed including 22 potential medication management problems, covering four domains; functional (7), organisational (7), medication adherence (6) and medication knowledge (2). Median scores were calculated with the interquartile range. In addition, cognitive function was assessed with the Mini-Cog and frailty using the Groningen Frailty Indicator.

Results: 188 MDD users and 230 non-MDD users were interviewed. MDD users were older, more often female and used more drugs. 42% of the MDD users was possibly cognitively impaired and 63% was assessed as frail compared to 20% and 27% respectively of the non-MDD users. MDD users had more potential organisational problems (3 vs. 1; $p < 0.01$), functional problems (2 vs. 1; $p < 0.01$), medication adherence problems (1 vs. 0; $p < 0.01$) and medication knowledge problems (1 vs. 0; $p < 0.01$) compared to non-MDD users. 70% of the MDD users scored six or more potential medication management problems while this was 22% among non-MDD users.

Conclusions: The majority of MDD systems were initiated for patients who experienced multiple potential medication management problems suggesting a decreased medication management capacity.

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Introduction

It is estimated that medication adherence to long-term therapies lies around 50%.[1] Non-adherence can be caused by a wide variety of reasons which can be divided into two major subgroups: intentional and unintentional non-adherence. Intentional non-adherent patients consciously decide to adapt their medication regimen. Unintentional non-adherent patients unconsciously fail to adhere to their medication regimen.[2] The capacity to adhere to the medication regimen may be diminished by a wide variety of reasons (e.g., a decline in cognitive function, complex dosing regimens, a change in appearance of outer packaging, impaired manual dexterity).[3,4]

Intentional non-adherence is best targeted with multiple component interventions focused on patient education and patients' behaviour.[2] For unintentional non-adherence more practical interventions may be more appropriate.[2,3,5] Especially older adults with polypharmacy and unintentional non-adherence might benefit from dosing aids. Dosing aids are intended to support patients with their medication use and improve the patients' medication adherence.[3,6-8] However, there are also concerns about the quality of drug treatment in patients who use dosing aids. Dosing aid users had a higher number of potential inappropriate medications and a reduced number of drug regimen changes. [9-11]

If patients have lost the capacity to manage their medication, health care professionals can decide to dispense the medication via a dosing aid. As the number of older adults with polypharmacy is increasing, the use of dosing aids is also rising. In the Netherlands, automated multidose drug dispensing (MDD) is preferably used when dosing aids are initiated by health care providers.[12] In an MDD system, all oral chronic medication intended for one dosing moment is automatically packed in plastic disposable bags. The content, patient information and designated time of intake is printed on the bag.[13]

MDD systems are relatively expensive compared to manual dispensing and should therefore be reserved for patients who have a decreased medication management capacity (MMC).[12] However, an unambiguous definition of a decreased MMC is lacking. In practice, a proposal to initiate an MDD system can be suggested by a variety of people (e.g., the patients, relatives, nurses, physicians or pharmacists). MDD systems are only reimbursed if the general practitioner (GP) agrees to start an MDD system. Various assessment tools have been evaluated in a systematic review, but none were recommended to be used in daily practice because of a low reliability and validity.[14] As a consequence, no guidelines or assessment tools are available for health care professionals to identify patients with a decreased MMC. Whether MDD systems

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are initiated in the appropriate patients is therefore unknown. The objective of this study was to compare potential medication management problems of patients who were about to start with an MDD system and patients who used manually dispensed medication in order to identify if the appropriate patients receive an MDD system.

Method

Study design

This was a case-control study performed in 44 community pharmacies in the Netherlands. The study was performed as part of a post academic training program in which the pharmacists participated. Eligible patients had to be over 65 years of age, home dwelling and use a minimum of five chronic prescription drugs. Patients receiving their medication already via an MDD system and patients receiving professional home care responsible for the medication administration were excluded. MDD users (cases) were scheduled to start an MDD system, but at the time of the interview still used manually dispensed drugs. Non-MDD users (controls) used manually dispensed drugs. Controls were selected by the participating pharmacies. Community pharmacists selected patients who met the inclusion criteria from their pharmacy information system. Thereafter, a random selection of ten patients was made using computer generated random numbers. From these 10 patients, pharmacists invited patients to participate until at least five control patients were included. If pharmacists were not able to include five eligible MDD patients, additional non-MDD users could be included. A teleconference was organized to inform participating pharmacists and ensure consistency during the interviews. Pharmacists received detailed instructions on how to conduct the semi-structured interview and avoid closed-end questions.[15] Additionally, pharmacists were instructed to inform the GP, after the patient's approval, in case any relevant health complaint was suspected during the interview. Patients were invited to participate by telephone by the pharmacist. Interviews were conducted at the patient's home.

Medication management capacity

Existing tools which assessed the patient's MMC were used to develop a comprehensive assessment tool.[16-20] Existing tools use various strategies to assess the patient's MMC including self-reported adherence, the ability to open medication vials, the ability to read and interpret medication labels and the ability to identify the medication in use. The design of the questionnaire was an iterative process of discussing and adjusting the questions. The first version of the questionnaire contained all used question from

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existing tools that assessed the patient's MMC. The questionnaire was supplemented with questions based on the Dutch guideline for patients using dosing aids.[12] The questionnaire was then tested in a pilot among current MDD users and controls. Undistinctive questions were deleted. Ambiguous questions were altered and clarified. Remaining questions were again tested in a pilot among current MDD users and non-MDD users. The final assessment tool contained 22 questions which covered four different domains; functional problems (7 questions), organisational problems (7 questions), medication adherence (6 questions) and medication knowledge (2 questions) (see Appendix 1). Answers were also considered correct if patients could not recall the exact indication (e.g., heart failure or myocardial infraction) but were able to give a more global indication (e.g., 'for the heart').[13] Questions were dichotomised and each scored one point if present. All interviews were conducted by the community pharmacist. During the interview, patients were asked about their opinion on different aspects of their capacity to manage their medication. If present, the patient's relative was also asked one question about their opinion on the patient's capacity to manage their medication. Additionally, the patient's GP was always asked about their opinion on the patient's capacity to manage his medication.

Cognitive function

The Mini-Cog was applied to explore the patient's cognitive function. The Mini-cog consists of a short memory test and a clock-drawing test (Appendix 2).[21] A low score (≤ 2 points) indicates a potential cognitive impairment. The Mini-Cog is easy to conduct and scored high on sensitivity and specificity compared to the MSSE.[22]

Frailty

The Groningen Frailty Indicator (GFI) was applied to assess patient's frailty (Appendix 3).[23,24] The GFI consists of 15 questions, which can all be scored one point. If scored four or more points patients were considered frail.

Ethics and confidentiality

Conform the Dutch Medical Research Involving Human Subjects Act (WMO) no formal ethical approval was needed to perform the study. The research protocol was approved by the Institutional Review Board of UPPER, division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University.[25] Patients signed informed consent before the interview was performed. In order to protect the patient's privacy only age, gender, and the pharmacy's study number was documented. Patients were assigned a unique study number (based on the pharmacy study number, age and consecutive number of inclusion). Pharmacy study numbers were unknown to the researchers, only to a study

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coordinator (third party) who did not have access to the questionnaire data. In contrast to the researchers, the study coordinator was able to link the study number to the unique internal pharmacy number in order to check for double patients. The researchers could only contact pharmacies through the study coordinator.

TABLE 1: Baseline characteristics

	MDD users (n=188)		Non-MDD users (n=230)		p-value
Female; *n (%)*	126	67	121	53	0.003[a]
Age; *median (IQR)*	80.5	76 – 85	76	71 – 81	< 0.001[b]
Number of drugs per patient; *median (IQR)*	8	7 – 11	7	6 – 9	< 0.001[b]
Number of manually-dispensed drugs per patient; *median (IQR)*	1	0 – 3	7	6 – 9	< 0.001[b]
Number of drugs in MDD; *median (IQR)*	7	5 – 8	-	-	-
Cognitive function and frailty					
Mini-Cog score ≤ 2; *n (%)*	78	42	45	20	< 0.001[a]
GFI score ≥ 4; *n (%)*	118	63	62	27	< 0.001[a]
Potential medication management problems					
Functional problems; *median (IQR)*	2	1 – 4	1	0 – 2	< 0.001[b]
Organisational problems; *median (IQR)*	3	2 – 4	1	1 – 2	< 0.001[b]
Adherence; *median (IQR)*	1	0 – 2	0	0 – 1	< 0.001[b]
Medication knowledge; *median (IQR)*	1	0 – 2	0	0 – 0	< 0.001[b]
Total potential medication management problems; *median (IQR)*	8	5 – 10	3	2 – 5	< 0.001[b]

IQR interquartile range; MDD multidose drug dispensing, GFI Groningen Frailty Indicator
[a] tested with Pearson Chi-square test
[b] tested with Mann-Whitney U test

Sample size calculation and statistical analysis

A mean number of 10.5 (SD 5.01) potential problems was found in the pilot study. To demonstrate an absolute difference between the two groups of 20% in the number of potential problems with a power of 80% and an alfa of 0.05, 90 patients in both groups were needed. In order to maintain the possibility to stratify on different patient characteristics (e.g., cognition and frailty) and to compensate for the possible dropout of pharmacists and potential issues with unevaluable data, we aimed to include 440 patients. All data were analysed using statistical software (SPSS version 23.0; SPSS Inc.,

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Chicago, IL, USA). Descriptive statistics were used for basic characteristics. Median scores with the interquartile range are presented. Continuous variables were tested with a Mann-Whitney U test. Dichotomous variables were tested using a Pearson Chi-square test. A Fleiss' kappa coefficient was calculated for inter-rater agreement between the estimation of the patient's relative and GP. The cut-off value for a decreased MMC was based on the optimal ROC curve.

Results

A total number 418 patients were included in the final analysis (188 MDD users and 230 non-MDD users). 15 included patients were excluded from the analysis because inclusion criteria were not met. MDD users were more often female, older and used more drugs compared to non-MDD users (see Table 1).

MDD users had more potential medication management problems (median 8; IQR 5 – 10) compared to the non-MDD users (median 3; IQR 2 – 5). Potential medication management problems were more prevalent among MDD users on all four domains as shown in Table 1. The cumulated score on all questions per patient is graphically presented in Figure 1. Scores on separate questions are shown in Appendix 1.

Among MDD users, 70% (n=132) had six or more potential problems. From MDD users with less than six potential problems (n=56), only 34% (n=19) of the patients or their relative, and 52% (n=29) of the GPs were of the opinion that the patient had lost the capacity to manage his medication (Table 2).

Among non-MDD users, 22% (n=50) of the patients scored six or more potential problems. Within this group, 30% (n=15) of the patients or their relative and 18% (n=9) of the GPs were of the opinion that the patient had lost the capacity to manage their medication (Table 2).

42% of the MDD users were assessed as cognitively impaired against 20% of the non-MDD users (OR 2.9; 1.9 – 4.5). Cognitively impaired patients had more potential medication management problems compared to patients with no cognitive impairment (median scores 8 vs. 4; $p < 0.01$). MDD users were assessed more often frail compared to non-MDD users (OR 4.3; 2.7 – 6.3). Frail patients had more potential medication management problems compared to non-frail patients (median scores 8 vs. 4; $p < 0.01$).

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TABLE 2: The number of patients with a decreased capacity to manage their medication according to the patient or their relative and the GP

	< 6 problems	≥ 6 problems	p-value
non-MDD users	**n = 180 (78%)**	**n = 50 (22%)**	
Estimation by the patient or their relative; *n (%)*	4 (2%)	15 (30%)	< 0.001
Estimation by the GP; n (%)	2 (1%)	9 (18%)	< 0.001
MDD users	**n = 56 (30%)**	**n = 132 (70%)**	
Estimation by the patient or their relative; *n (%)*	19 (34%)	92 (70%)	< 0.001
Estimation by the GP; n (%)	29 (52%)	112 (85%)	< 0.001

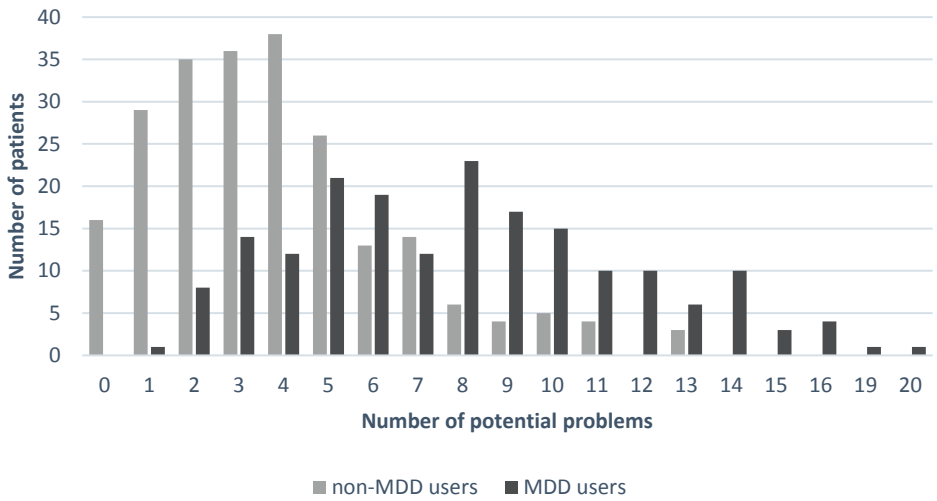

FIGURE 1: Number of patients with scores on all potential medication management problems

Using a different cut-off value of five or seven did not substantially change the number of patients who were classified as receiving their medication via an inappropriate method of dispensing. A cut-off value of 5 resulted in a sensitivity of 74% and specificity of 67%. A cut-off value of 6 resulted in a sensitivity of 70% and specificity of 78%. A cut-off value of 7 resulted in a 60% sensitivity and specificity of 84%. Inter-rater agreement between relatives and GPs was high (k=0.898).

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Discussion

This study showed that the majority of MDD systems are initiated for patients who are likely to have a decreased MMC. Potential medication management problems were more prevalent among MDD users compared to non-MDD users and were related to all different domains (functional, organisational, medication adherence and medication knowledge). MDD users were also older, used more medication, were more often cognitively impaired and frail.

On the other hand, there is also a non-negligible group of MDD users (30%) for who the start of an MDD system might be inappropriate. These patient had five or even less potential medication management problems. Among these patients, the majority estimated they had not lost the capacity to manage their medication. Although the initiation of an MDD system in these patients seems questionable, some patients may still need an MDD system because of a specific problem. For instance, patients who lost the ability to identify their medication correctly, may not be capable to adhere to a complex medication regimen. With the use of an MDD system this specific problem might be overcome.

Opposite of the possible overuse of MDD systems, also underuse probably occurs. 22% of the non-MDD users had six or more potential medication management problems. From these patients, about one third indicated indeed to have lost the capacity to manage their medication. To identify these patients health care professionals must screen the MMC among older adults with polypharmacy. Especially if there are cognitively impaired or frail.

The development of an assessment tool to identify patients with a decreased MMC is difficult as a gold standard is lacking. In our study, we used a score of six or more potential medication management problems as an indicator that the patient had a decreased MMC. This cut-off value remains arbitrary as there is no objective method to assess the MMC. Using different cut-off values resulted in a 10% increase or decrease of patients who received the appropriate method of dispensing. Using a higher cut-off value of seven would result in more MDD users for who an MDD system might be inappropriate. But on the other hand, less non-MDD users should receive an MDD system.

More importantly, when choosing between MDD and manual dispensing, health care professionals have to balance the patient's self-efficacy, patronizing patients, the higher costs and the patient's MMC. As shared decision-making is expected to improve medication adherence, the patient's opinion must be taken into account in the decision

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to start an MDD system.[26,27] MDD systems must not be initiated in patients who don't agree with the initiation of an MDD system, even if multiple medication management problems are prevalent. On the other hand, health care professional must be able to initiate an MDD system in patients who state they have lost the capacity to manage their medication but only experience a few medication management problems. The proposed questionnaire is therefore merely intended to support health care professionals to identify patients with a potentially decreased MMC. It must explicitly not be decisive in the decision to start an MDD system.

This study was the first in which patients were included who were about to start with a dosing aid, but at the time of the interview still used manually dispensed medication. This enabled us to compare medication management problems between a high risk population (MDD users) and a randomly selected population (non-MDD users). Because 44 different community pharmacies throughout the Netherlands participated in the study, the results are well generalizable to the Dutch population. A third strength of the study was the comprehensive character of the questionnaire. The questionnaire was developed with a broad scope combining different elements which might be of influence on the patient's MMC. In addition to the questionnaire, the patient, or their relative, and the GP were asked about their opinion of the patient's capacity to manage his medication. As a result three different signs for a decreased medication management could be combined, firstly the start of an MDD system, secondly the score on the questionnaire and thirdly the patient's or their relative's estimation.

The study also had some limitations. Firstly, MDD users were invited to participate in the study if the decision was already made to start an MDD system. As a consequence, patients or their relatives and GPs might be inclined to confirm that the patient lost the capacity to manage his medication. This bias was only present in MDD users and not among non-MDD users as they were randomly selected. Among the non-MDD users the opposite might be the case, GPs could be unaware of a possible decreased MMC. Secondly, basic characteristics between the MDD users and non-MDD users did not match on age, gender and number of drugs. Non-MDD users were deliberately not matched on these characteristics, as these characteristics might be a determinant for a decreased MMC. Thirdly, patients with homecare responsible for the medication administration were excluded as Dutch guidelines states that patients receiving homecare should always receive medication via an MDD system. Especially these patients are expected to have multiple medication management problems. Including this group would probably result in even more MDD users with multiple medication management problems.

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Finally, in this study potential medication management problems leading to the start of an MDD system were identified, whether the start of an MDD system resolved these problems is unknown. This must elucidated in further research.

Conclusions

For the majority of MDD users, the initiation of an MDD system was appropriate as these patients experienced multiple potential medication management problems suggesting a decreased MMC. However, for a minority of MDD users the start of an MDD system might be questionable according to the limited number of medication management problems. On the other hand, there is a group of non-MDD users who seem to have a decreased MMC, but still use manually dispensed medication. These patients might benefit from an MDD system. To identify these patients, health care professionals must screen older patients with polypharmacy on their MMC.

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Authors' contributions

B. Mertens, H.F. Kwint, and M.L. Bouvy were responsible for the study concept and design. B. Mertens performed the statistical analysis. All authors contributed to interpretation and writing of the manuscript and approved the final manuscript for submission.

Conflicts of Interest

B. Mertens received an unconditional grant for a PhD project to multidose drug dispensing to conduct this research. The other authors declare no conflict of interest relevant to this study.

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APPENDIX 1: Scores on all separate questions

		MDD users (n=188)		Non-MDD users (n=230)			
Domain	**Question**	**Yes**	**No**	**Yes**	**No**	**OR**	**95%CI**
Adherence	Patient takes all medication on the designated time of intake		62 (33%)		30 (13%)	3,3 *	2,0 – 5,4
Adherence	Patient takes medication of one dosing moment divided over the day	46 (24%)		41 (18%)		1,5	0,9 – 5,4
Adherence	Patient takes the right amount of medication each dosing moment		19 (10%)		9 (4%)	2,7 *	1,2 – 6,2
Adherence	Patient takes the medication the right amount of times per day		33 (18%)		21 (9%)	2,1 *	1,2 – 3,7
Adherence	Patient adheres to special instructions		38 (21%)		22 (10%)	2,4 *	1,4 – 4,3
Adherence	Patient forgets medication on a regular basis	83 (45%)		27 (12%)		5,9 *	3,6 – 9,7
Functional	Patient is able to read the label		37 (20%)		14 (6%)	3,8 *	2,0 – 7,2
Functional	Patient uses supportive reading tools to read the label	108 (57%)		141 (61%)		0,9	0,6 – 1,3
Functional	Patient experiences problems in daily life because of poor vision	47 (25%)		19 (8%)		3,7 *	2,1 – 6,6
Functional	Patient can correctly explain the information of a random chosen drug label		37 (20%)		9 (4%)	6,0	2,8 – 12,8
Functional	Patient has troubles with the packaging of the medication	66 (35%)		39 (17%)		2,7 *	1,7 – 4,2
Functional	Patient finds it difficult to manage his drug regimen	113 (26%)		26 (11%)		12,0 *	7,3 – 19,9
Functional	Patient has reduced manual dexterity	81 (56%)		56 (24%)		2,4 *	1,6 – 3,6
Organisational	Patient finds it difficult to order the medication in time	98 (52%)		29 (13%)		7,5 *	4,7 – 12,2
Organisational	Patient has medication at home for a period longer than three months	45 (24%)		15 (7%)		4,5 *	2,4 – 8,4
Organisational	Patient stores his medication on multiple places	80 (43%)		81 (35%)		1,4	0,9 – 2,0
Organisational	Patient has multiple generic brands at home from one drug	73 (39%)		66 (29%)		1,6 *	1,1 -2,4
Organisational	Patient stores his medication according to the storing conditions		21 (11%)		7 (3%)	4,0 *	1,6 – 9,5
Organisational	Patients has ceased medication at home	95 (51%)		56 (24%)		3,2 *	2,1 – 4,8
Organisational	Patient finds it difficult when the appearance of a drug changes	116 (62%)		110 (48%)		1,8 *	1,2 – 2,6
Medication knowledge	Patient can recall the correct indication of > 75% of their medication		97 (52%)		35 (15%)	5,9 *	3,8 – 9,4
Medication knowledge	Patients designates all medication correctly		108 (58%)		35 (16%)	7,5 *	4,7 – 11,9

*represent significant values with a p-value of < 0.05

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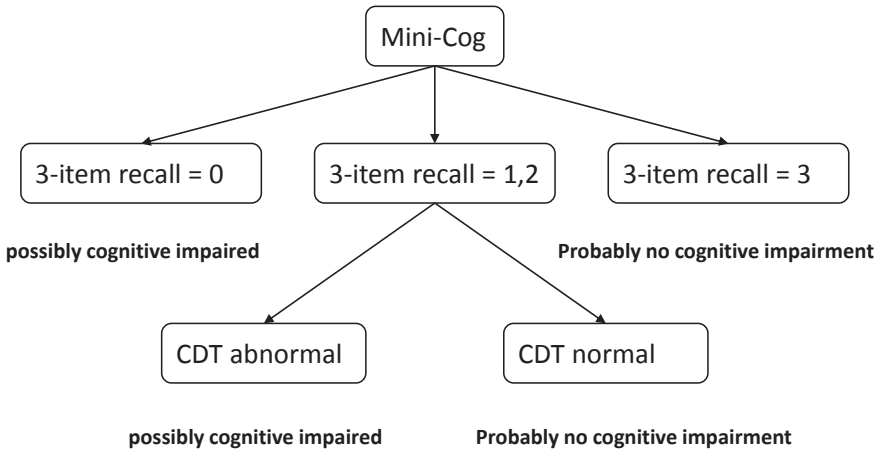
APPENDIX 2: Mini-Cog

Algorithm of the Mini-Cog. Items to be recalled: apple, coin and table. CDT: clock drawing test. Adapted from Borson et al.[21]



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APPENDIX 3: Groningen Frailty Indicator, adapted from Steverink et. al.[23]

	For questions 1-4: Is the patient able to carry out these tasks without any help? (The use of help resources such as walking stick, walking frame, wheelchair, is considered independent)	Yes	no	
1	Shopping		✓	
2	Walking around outside (around the house or to the neighbours)		✓	
3	Dressing and undressing		✓	
4	Going to the toilet		✓	
5	What mark does the patient give himself/herself for physical fitness? (scale 0 to 10) 0 – 6 = 1 point 7 – 10 = 0 points			
		Yes	no	
6	Does the patient experience problems in daily life due to poor vision?	✓		
7	Does the patient experience problems in daily life due to being hard of hearing?	✓		
8	During the last 6 months has the patient lost a lot of weight unwillingly?	✓		
	(3 kg in 1 month or 6 kg in 2 months)	✓		
9	Does the patient take 4 or more different types of medicine?	✓		
		Yes	Sometimes	No
10	Does the patient have any complaints about his/her memory?	✓	✓	
11	Does the patient sometimes experience an emptiness around him/her?	✓	✓	
12	Does the patient sometimes miss people around him/her?	✓	✓	
13	Does the patient sometimes feel abandoned?	✓	✓	
14	Has the patient recently felt downhearted or sad?	✓	✓	
15	Has the patient recently felt nervous or anxious?	✓	✓	

✓ indicates one point
If scored ≥ 4 points, the patient is assessed as frail

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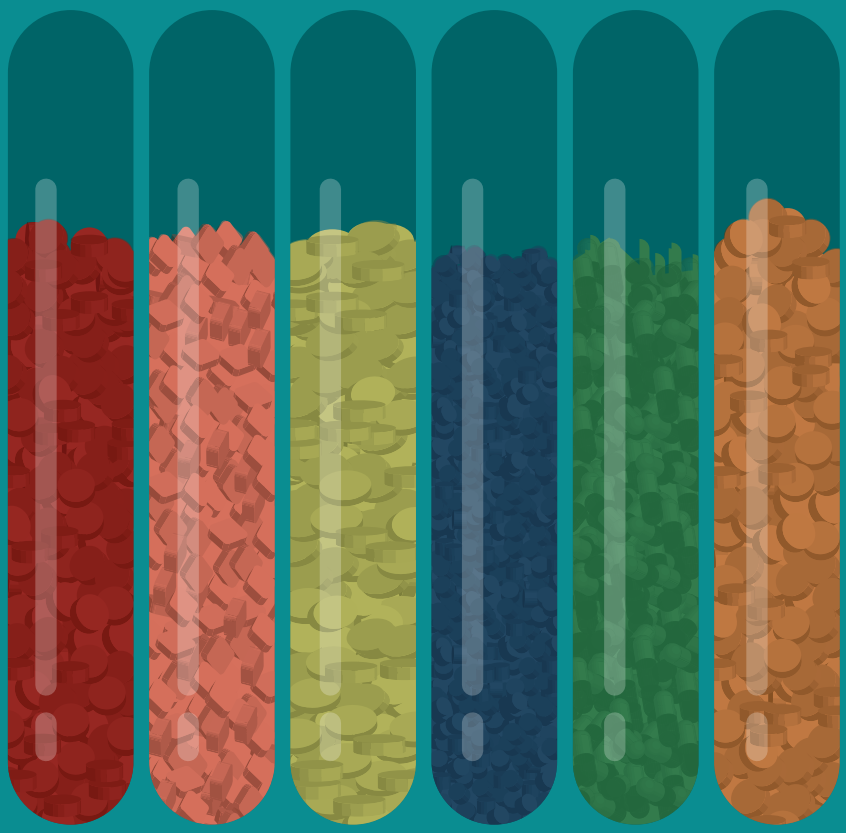

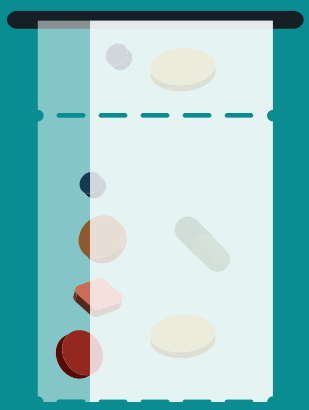

Chapter 3

Potentially inappropriate medication use before and after the start of multidose drug dispensing systems in older people: a longitudinal study

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Submitted

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Abstract

Aim: To assess the number of drugs and the prevalence of potentially inappropriate medications (PIMs) before and after the initiation of multidose drug dispensing (MDD) in older patients.

Method: From the Dutch PHARMO Database Network, all new MDD users in 2015 ≥ 65 years of age were identified and matched (1:1) to non-MDD users by age, sex and number of dispensed drugs (ATC-5 level) in the weeks 40 – 28 before the index date. The quality of drug treatment before and after the initiation of the MDD system was assessed using the indicators for PIMs from the Swedish National Board of Health and Welfare.

Results: 8121 MDD patients were identified and matched. 7132 MDD patients and 7306 control patients were included in the analyses. Mean age was 81.0 and 60% was female. MDD patients used more drugs compared to controls (4.5 vs. 4.0; $p < 0.01$) in the weeks 40 – 12 before the initiation of an MDD system. The proportion of patients using: *ten or more drugs* (10.6% vs 7.1%; $p < 0.01$), *antipsychotics* (3.9% vs. 1.1%; $p < 0.01$), *anticholinergics* (7.9% vs. 5.0%; $p < 0.01$) and ≥ *3 psychotropics* (2.2% vs. 0.8%; $p < 0.01$) was higher among MDD patients. Around the initiation of the MDD system, the number of drugs and prevalence of PIMs increased sharply among MDD patients, whereas it remained stable among control patients ($p < 0.01$), with the exception of the use of *long acting benzodiazepines* ($p = 0.72$). The increase in the number of drugs and prevalence of PIMs started already before the initiation of the MDD system.

Conclusion: This study showed that patients with an MDD system have a higher number of drugs and prevalence of PIMs compared to non-MDD users with a peak around the start of MDD. This suggests a sudden change in the patient's health status that may cause the initiation of an MDD system.

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Introduction

In automated multidose drug dispensing (MDD) systems all drugs intended for one dosing moment are gathered in disposable bags and labelled with patient data, drug contents, the date and time for intake.[1,2] MDD systems are mostly used in patients aged ≥ 65 years with polypharmacy and in patients with complex psychiatric problems.[1,3] These patients often experience problems managing their medications. MDD systems are expected to support these patients with their medication regimen.[2-4]

MDD systems are assumed to improve adherence, reduce medication errors and decrease waste of unused drugs.[4-10] However, evidence is limited and the results on health outcomes are not very robust.[4,11,12] But even without robust evidence, the use of dosing aids, including MDD systems, is rapidly increasing.[13-15] In the Netherlands, already 25% of the patients over 80 years of age receive their medication via an MDD system.[16] Despite the intentions of better patient care with MDD systems, epidemiologic studies suggest an association between the use of MDD systems and poor quality of drug treatment.[6,17-19] Patients who use MDD systems or other multicompartment compliance aids have a high prevalence of potentially inappropriate medications (PIMs).[13] Users of MDD systems have been associated with fewer changes in drug treatment and with an increased overall number of drugs compared to users of manual dispensed medication. This suggests limited reconsideration of drug treatment after the initiation of MDD.[5] In contrast, a Finnish study suggested that the initiation of an MDD system combined with a prescription review resulted in a reduction in drug use.[20]

To date, most studies used a cross-sectional design. The one study that used a longitudinal study design did not incorporate control patients.[6] As a consequence, it is unknown if patients who start with an MDD system differ already before the initiation of an MDD system from control patients in the number of drugs and use of PIMs. Patients who start with MDD system are likely to be older, more fragile, more often cognitively impaired and use more drugs compared to users of manual dispensed medication.[3,20] The aim of our study was to assess the number of drugs in use and the prevalence of PIMs before and after the initiation of an MDD system compared to matched controls.

Methods

Data extraction

For this retrospective cohort study, data were used from the Out-patient Pharmacy Database of the PHARMO Database Network. This database comprises pharmacy

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dispensing records from around 4.2 million Dutch patients, which is around 25% of the Dutch population. The database contains information on type of product, anatomic therapeutic chemical (ATC) code, dosage, dosage regimen, date of dispensing, quantity dispensed, and prescriber specialty.

Study population

Patients ≥ 65 years of age who started with an MDD system were matched to controls. The use of an MDD system is not formerly registered in the PHARMO Database Network. Because MDD patients receive their medication per week (for 1, 2, or a maximum of 3 weeks), patients were identified as new MDD user if they met the following criteria; (1) at least 2 drugs (ATC codes J01: antibiotics and H02: corticosteroids were excluded) were dispensed on the same date for a duration of 7, 14 or 21 days in 2015. The duration was calculated by dividing the number of dispensed dosing units by their prescribed daily dose (PDD); (2) patients received at least 4 repeat dispensings of these drugs in the next 12 months; (3) patients did not meet these criteria in 2014. Identified MDD patients received an index date (start date MDD system) which was the first day at which the patient received the medication for a duration of 7, 14 or 21 days.

Matching was performed in three steps. First, MDD patients were matched (1:1) with control patients by age and sex. Controls received the index date from their matched MDD patient. Second, the number of different dispensed drugs (ATC-5 level) were calculated over a 12 week period (from 40 to 28 weeks) preceding the index date. A period of 12 weeks was chosen as chronic prescription drugs are dispensed for a maximum period 12 weeks. Third, MDD patients and controls were matched on the number of different drugs dispensed.

Analysed period

Pharmacy dispensing records of all patients over a period of exactly two years (365 days before and 365 days after the patient's index date) were received. As noted earlier, chronic prescription drugs are usually dispensed for a period of 12 weeks. As a consequence, the number of patients with at least one dispensed drug gradually increased during the first 12 weeks of the two years study period. Therefore, the first three months were excluded from the analyses. To analyse an equal time period before and after the index date, the last 12 weeks of the two years study period were also discarded. The total study period for every patient was divided into 7-day intervals. The medication exposure was assessed for all intervals based on the dispensing date and the intended duration of use; i.e. both dispensings within the interval as earlier dispensings with a duration of use covering the interval contributed to patient's exposure. The intended duration was

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calculated by dividing the number of dispensed dosing units by the PDD. If the PDD was missing, the defined daily dose (DDD) was used. For the before and after comparison of the increase in the mean number of drugs and the prevalence of PIMs, the 12 weeks preceding and after the index date were excluded from the analyses (see Figure 1). This resulted in a period before the index date (-40 to -12 weeks) and after the index date (+12 to +40 weeks). Patients were included in the analyses if they had at least one dispensed drug in both periods. For the graphical presentation, all time intervals were included in the analyses.

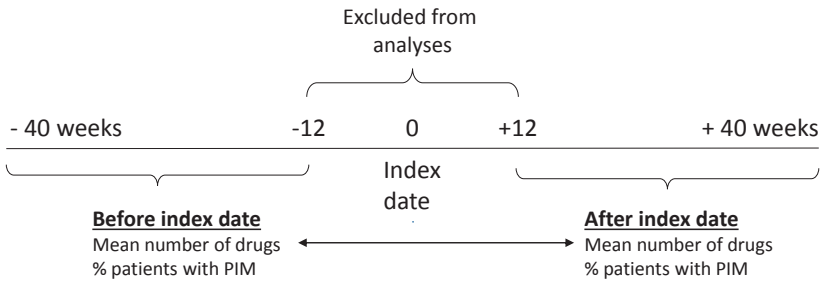

FIGURE 1: Schematic presentation of the time period used for the calculation of the mean number of number of drugs and prevalence of PIMs before and after the initiation of an MDD system.

Outcome

To enable comparison of our results with earlier performed studies, the number of drugs in use and quality of drug treatment was assessed using the PIM Indicator list of The Swedish National Board of Health and Welfare (Appendix 1).[5,6,13] Drugs that were not on the Dutch market or recommended in Dutch guidelines as first choice therapy were excluded (Appendix 1).

Statistical analyses

Data were analysed using SAS Enterprise Guide 9.4 (SAS Institute Inc, Cary, NC, USA). Descriptive statistics were used for baseline characteristics. Continuous variables were tested using a student's t-test. Non-paired dichotomous variables were tested using a Pearson chi-square test. Paired dichotomous variables were tested with a McNemar's test.

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Ethics approval

In accordance with the Dutch Medical Research Involving Human Subjects Act, no ethical approval was needed for this retrospective database study. All data in the PHARMO Database Network are anonymised. The database does not include any information allowing identification of individual patients.

Results

A total of 16496 patients initiated an MDD systems were identified, from who 8121 could be matched to 8121 controls. From the matched MDD patients and control patients respectively 88% (7132) and 90% (7306) had at least one dispensing before and after the index date and were included in the analyses. 60% of the patients were female and the mean age was 81.0 (SD 7.0) with no differences between MDD patients and control patients. Control patients were dispensed more temporary medications (J01, S01, R01, R03, D07) compared to MDD patients in the 12 weeks (-40 to -28) used for matching (Appendix 2). The mean number of drugs over the time intervals -40 to - 12 was higher for the MDD patients (4.5 [95%-CI 4.4 – 4.5]) compared to the control patients (4.0 [95%-CI 3.9 – 4.0]). MDD patients used more PIMs before the start of the MDD system, with the exception of the *long acting benzodiazepines* (Table 2). MDD patients differed from control patients in the type of medication used. At baseline (40 weeks before the index date), MDD patients used more antithrombotic agents, antidiabetics, diuretics, psycholeptics and psychoanaleptics (Table 1).

TABLE 1: Top-10 most frequently used drugs 40 weeks before index date

	MDD users N = 7132	Non-MDD users N = 7306	p-value
B01 - Antithrombotic agents*; %*	48.6	44.0	**< 0.01**
C09 - Agents acting on the renin–angiotensin system*; %*	45.2	45.7	0.39
C10 - Lipid modifying agents*; %*	41.0	41.6	0.65
C07 - Beta blocking agents*; %*	37.3	36.9	0.42
A02 - Drugs for acid related disorders*; %*	36.6	36.2	0.97
A10 - Drugs used in diabetes*; %*	29.2	18.4	**< 0.01**
C03 - Diuretics*; %*	28.8	26.5	**0.03**
C08 - Calcium channel blockers*; %*	19.3	19.0	0.13
N05 - Psycholeptics*; %*	16.8	12.6	**< 0.01**
N06 - Psychoanaleptics*; %*	11.7	6.7	**< 0.01**

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The number of drugs and prevalence of PIMs is graphically depicted in Figure 2. For the non-matched MDD patients, comparable patterns were seen, only the mean number of drugs and PIMs were higher. MDD patients used more drugs after the initiation of the MDD system compared to the period before ($p < 0.01$). The increase in the number of drugs and prevalence of PIMs started before the initiation, peaked around the index date and stabilized after the initiation of the MDD system. The increase in the proportion of patients using *ten or more drugs* ($p < 0.01$), *antipsychotics* ($p < 0.01$), *anticholinergics* ($p < 0.01$) and *the combination of ≥ 3 psychotropics* ($p < 0.01$) was higher after the initiation of an MDD system compared to the control patients (Table 2). The highest increases after the initiation of an MDD system were observed for antithrombotic agents (+ 30%), drugs for acid related disorders (+ 25%) and analgesics (+18%) (Figure 3).

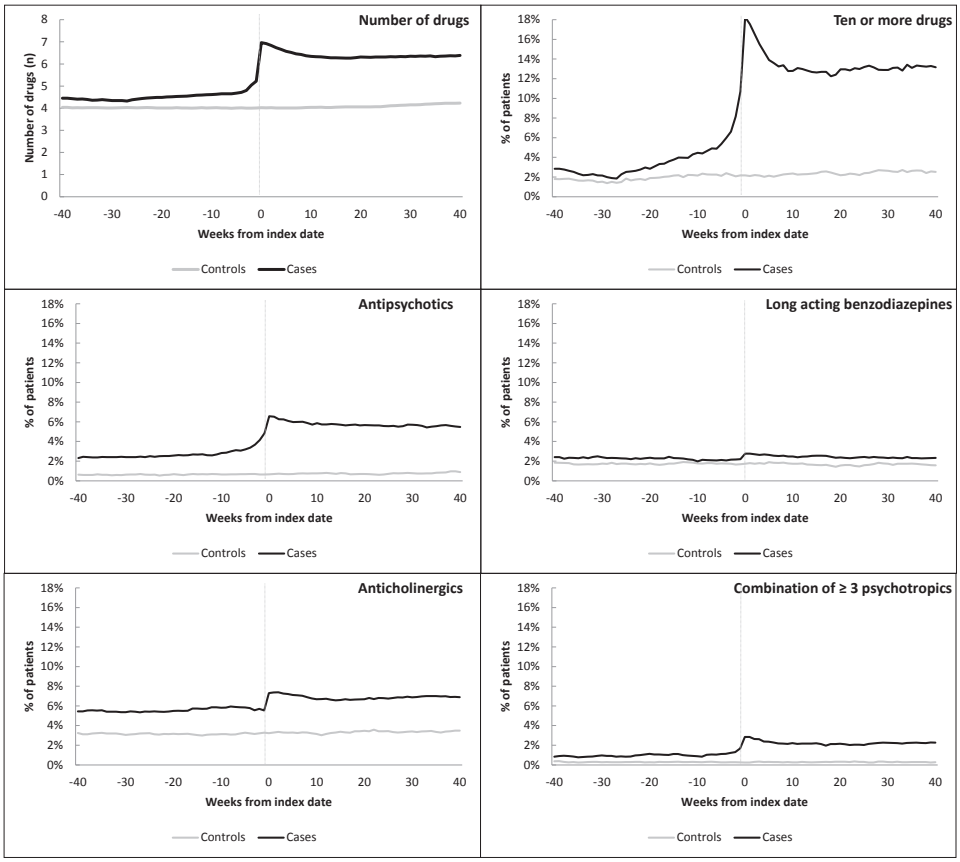

FIGURE 2: Graphical presentation of the mean number of drugs and the percentage of patients with PIM per week.

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TABLE 2: Mean number of drug used and the percentage of patients with PIM before the index date, after the index date and the delta between before and after the index date.

	Before the index date			After the index date			Δ between before and after		
	MDD users	Non-MDD users	p-value	MDD users	Non-MDD users	p-value	MDD users	Non-MDD users	p-value
All patients	**n=7132**	**n = 7306**		**n=7132**	**n = 7306**		**n=7132**	**n = 7306**	
Number of drugs; *mean (SD)*	4.5 (2.2)	4.0 (2.5)	**< 0.01**	6.1 (2.6)	4.1 (2.4)	**< 0.01**	1.6 (2.4)	0.2 (1.1)	**< 0.01**
Ten or more drugs; *% (n)*	10.6 (759)	7.1 (522)	**< 0.01**	28.7 (2043)	9.4 (688)	**< 0.01**	18.0 (1434)	2.3 (166)	**< 0.01**
Antipsychotics; *% (n)*	3.9 (281)	1.1 (81)	**< 0.01**	8.5 (609)	1.6 (117)	**< 0.01**	4.6 (328)	0.5 (36)	**< 0.01**
Long acting benzo's; *% (n)*	3.7 (266)	3.2 (232)	0.07	3.7 (262)	3.2 (234)	0.12	0.0 (-4)	0 (2)	0.72
Anticholinergics; *% (n)*	7.9 (561)	5.0 (364)	**< 0.01**	9.0 (645)	5.3 (388)	**< 0.01**	1.2 (84)	0.3 (24)	**0.02**
≥ of 3 psychotropics; *% (n)*	2.2 (158)	0.8 (57)	**< 0.01**	3.8 (274)	0.9 (63)	**< 0.01**	1.6 (116)	0.1 (6)	**< 0.01**
65 - 79 years of age	**n=2704**	**n = 2818**		**n=2704**	**n = 2818**		**n=2704**	**n = 2818**	
Number of drugs; mean (SD)	4.5 (2.3)	3.9 (2.3)	**< 0.01**	6.4 (2.7)	4.0 (2.4)	**< 0.01**	1.9 (2.5)	0.1 (1.0)	**< 0.01**
Ten or more drugs; % (n)	12.5 (339)	7.5 (211)	**< 0.01**	33.4 (903)	9.3 (261)	**< 0.01**	20.9 (564)	1.8 (50)	**< 0.01**
Antipsychotics; % (n)	5.5 (149)	1.1 (30)	**< 0.01**	10.5 (285)	1.2 (33)	**< 0.01**	5.0 (136)	0.1 (3)	**< 0.01**
Long acting benzo's; % (n)	4.4 (120)	3.4 (96)	**0.05**	4.7 (126)	3.3 (93)	**0.01**	0.2 (6)	- 0.1 (-3)	0.12
Anticholinergics; % (n)	8.5 (230)	5.2 (145)	**< 0.01**	10.4 (280)	5.8 (164)	**< 0.01**	1.9 (50)	0.7 (19)	0.06
≥ of 3 psychotropics; % (n)	3.7 (101)	0.8 (22)	**< 0.01**	6.1 (165)	0.7 (20)	**< 0.01**	2.4 (64)	- 0.1 (-2)	**< 0.01**
≥ 80 years of age	**n=4428**	**n = 4488**		**n=4428**	**n = 4488**		**n=4428**	**n = 4488**	
Number of drugs	4.5 (2.1)	4.1 (2.2)	**< 0.01**	5.9 (2.5)	4.2 (2.3)	**< 0.01**	1.5 (2.3)	0.2 (1.1)	**< 0.01**
Ten or more drugs; *% (n)*	9.5 (420)	6.9 (311)	**< 0.01**	25.8 (1140)	9.5 (427)	**< 0.01**	16.3 (720)	1.8 (116)	**< 0.01**
Antipsychotics; *% (n)*	3.0 (132)	1.1 (51)	**< 0.01**	7.3 (324)	1.9 (84)	**< 0.01**	4.3 (192)	0.7 (33)	**0.04**
Long acting benzo's; *% (n)*	3.3 (146)	3.0 (136)	0.47	3.1 (136)	3.1 (141)	0.85	- 0.2 (10)	0.1 (5)	0.22
Anticholinergics; *% (n)*	7.5 (331)	4.9 (219)	**< 0.01**	8.2 (365)	5.0 (224)	**< 0.01**	0.7 (34)	0.1 (5)	0.15
≥ of 3 psychotropics; *% (n*	1.3 (57)	0.8 (35)	**0.02**	2.5 (109)	1.0 (43)	**< 0.01**	1.2 (52)	0.2 (8)	**< 0.01**

* statistical differences are shown in bold

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The increase in the mean number of drugs and the use of *ten or more drugs* and *the combination of ≥ 3 psychotropics* was higher among patients aged 65 – 79 years compared to patients ≥ 80 years of age (Table 2).

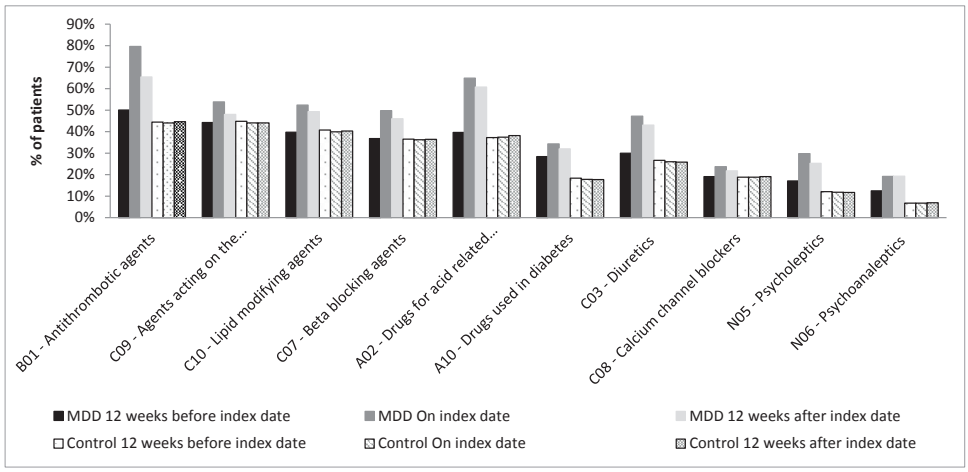

FIGURE 3: The top 10 drugs with the highest increase in number of users on the index date compared to 12 weeks before the index date.

Discussion

This study shows that the number of drugs in use and the prevalence of PIMs is sharply increasing around the initiation of the MDD system after a gradual increase in the months before. MDD patients used more drugs and PIMs already before the initiation of an MDD system compared to control patients. After the sharp increase around initiation of MDD system, the number of drugs and prevalence of PIMs decreased slightly and stabilized.

It has previously been suggested that the use of MDD systems may increase the number of drugs and PIMs.[5,6,17] The comparison of the baseline characteristics of patients initiating an MDD system and control patients suggest another explanation. The number of drugs and two PIMs (*ten or more drugs* and *antipsychotics*) were already gradually increasing several months before the actual start of the MDD system. Around the actual initiation of the MDD system, a peak on all indicators is seen, suggesting that a major part of these patients experienced an acute worsening in health status (e.g., a clinical event).

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This hypothesis is underlined by the sharp increase in the proportion of patients that used specific drugs such as antithrombotics and antipsychotics which could indicate an acute vascular event or delirium respectively. This change in health status and the concomitant increase in the number of drugs may necessitate the initiation of an MDD system. After the initiation of the MDD system, the number of drugs and prevalence of PIMs decreased and stabilized on a new plateau which is higher compared to the period before the MDD system. This suggests that initiation of MDD systems in itself is not the cause of the increase in the number of drugs or PIMs.

Wallerstedt et al. also explored the patient's medication patterns before and after the initiation of an MDD system, although they did not use a control group.[6] Both studies have many similar findings, but differed on two important aspects. In the study of Wallerstedt et al., the prevalence of most PIMs was higher before the initiation of the MDD system and increased more compared to our study. For instance, the PIM *ten or more drugs* increased from 10% before the MDD system to 25% after the MDD system versus 3% to 13% in our study. Also *the combination of ≥ 3 psychotropics* increased from 4% before the MDD system to 13% after the MDD system in the study of Wallerstedt et al. versus 2% to 3% in our study. This suggests that MDD systems are used more frequently for psychiatric patients in Sweden compared to the Netherlands. In our data, however, not all patients in psychiatric and geriatric hospitals will be captured as the community pharmacy will not always be the supplier of institutionalized patients. A second difference is the pattern after the initiation of the MDD system. In the study of Wallerstedt et al., the increment in the number of drugs continued while in our study it stabilized. This may be caused by a difference in organisation of care in the Netherlands compared to the organisation of care in Sweden at the time of both studies.[15] In the Netherlands, clinical medication reviews have been implemented on a large scale over the past years.[21,22] Patients with an MDD system are at high risk for drug related problems and eligible for clinical medication reviews.[23,24] A Finnish database study showed that a medication review at the start of an MDD system, can reduce drug use among MDD patients.[20] Additionally, the Dutch guideline which describes the care process for patients with an MDD system, obligates a periodically authorization of the prescriptions by the patient's GP, at least once a year.[1] This moment of authorization is frequently used to critically review the patient's medication. The combination of both the implementation of medication reviews and periodically authorization of the medication might explain the observed difference.

Despite matching on the number of drugs, MDD patients differed from control patients, already before the initiation of an MDD system. MDD patients used more drugs and more PIMs. This can be explained by two causes. First, controls used more temporary

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medication like antibiotics, ophthalmologicals and topical corticosteroids. For the matching, the number of different dispensed drugs were calculated, not the mean medication exposure over the 12 weeks. Second, the analysed period differed. For the matching a period of 12 weeks was used, whereas for the mean number of drugs in the study a period of 28 weeks was used. The number of drugs was already increasing in the MDD patients in these 28 weeks. Thereby, the mean number of drugs was also higher for the MDD patients.

Patients aged 65 – 79 years had a higher increase in number of drugs and PIMs compared to patients aged ≥ 80 years of age. An observation which has been reported in other studies.[13,18] The initiation of an MDD system in these patients might be less 'event driven' as the increase in the number of drugs was lower. Gradually, patients lose the ability to manage the medication and an MDD system is initiated. In patients aged 65 – 79 years, initiation of an MDD system may be caused more often by a clinical event leading to a higher increase in the number of drugs and PIMs and, concomitantly, the initiation of an MDD system.

All PIMs clearly peaked around the index date of the MDD system. In the next 12 weeks, this peak slowly declined. This is comparable to the pattern shown by Wallerstedt et al. and could be explained by two causes. First, when patients experience a clinical event, new medication is added. Second, the patient's previous medication is replaced. New medication is prescribed and old medication ceased. In the period before the MDD system, patients received their medication for a duration of 12 weeks. As the medication exposure was based on the amount of drugs dispensed earlier, it could take up to 12 weeks until a ceased drug no longer contributes to the drug exposure. The peak is therefore, at least, partly artificial.

Our study had some particular strengths. First, the longitudinal design enabled analyses within the same population. Second, we compared the medication patterns with a control group matched on patients' age, sex, and number of drugs. Third, the PHARMO Database Network contains drug dispensing records of 25% of the Dutch population and is representative for the whole population. Therefore, it can be assumed that our findings are generalizable to patients ≥ 65 years of age who start with an MDD system.

Our study had also some potential limitations. First, the selection of the MDD patients was based on a self-developed algorithm. We checked the accuracy of the algorithm by manually checking 100 randomly chosen patients. Based on the dispensing data, all patients were users of an MDD system. Second, the analysed period was relatively short. Possibly, the number of drugs and PIMs might start to increase 40 weeks after the

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initiation of the MDD system. However, in the study of Wallerstedt et al., the number of drugs and PIMs were already increasing shortly after the initiation of the MDD system. Third, not all matched MDD patients and controls were included in the analyses. It was unknown which MDD patient was matched to which control patient As a result, not all MDD patients had their matched control included in the analyses. Last, controls could only be matched for 49% of the new MDD users. However, the medication patterns for the non-matched MDD were comparable with the matched MDD patients. However, the non-matched MDD patients were older and used more drugs compared to the matched cases. The mean number of drugs and PIMs for MDD patients would even be higher with these patients included.

Conclusions

This study shows that patients who initiated an MDD system differ from control patients in the number of drugs and prevalence of PIMs, already before the initiation of an MDD system. The number of drugs and PIMs slowly increase during the months before the initiation of the MDD system and peaks around the start. This suggests a change in the patient's health status that causes the initiation of an MDD system.

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Competing interest

B. Mertens received an unconditional grant for his PhD project about multidose drug dispensing to conduct this research. The other authors declare no conflict of interest relevant to this study.

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APPENDIX 1. Included and excluded PIMs from Wallerstedt et al.[6]

Included PIMs from Wallerstedt et al.

PIMs	Class	ATC
Ten or more drugs	All drugs	
Three or more psychotropics	Antipsychotics	N05A
	Anxiolytics	N05B
	Hypnotics and sedatives	N05C
	Antidepressants	N06A
Long-acting benzodiazepines	Diazepam	N05BA01
	Nitrazepam	N05CD02
	Flunitrazepam	N05CD03
	Chlordiazepoxide	N05BA02
	Flurazepam	N05CD01
	Dipotassium clorazepate	N05BA05
	Bromazepam	N05BA08
	Alprazolam	N05BA12
	Clobazam	N05BA09
	Clonazepam	N05BA09
Drugs with anticholinergic effects	(Anticholinergic) drugs for functional gastrointestinal disorders	A03AB, A03BA, A03BB
	(Anticholinergic) antiemetic's	A04AD01
	Antiarrhythmics class Ia	C01BA
	Urinary antispasmodics	G04BD
	Anticholinergics (anti-Parkinson drugs)	N04A
	Low potency antipsychotics	N05AA, N05AF03
	Hydroxyzine	N05BB01
	TCAs (without nortriptyline)	N06AA09, N06AA12, N06AA02, N06AA04, A06AA21, N06AA16
	Antihistamines	R06AB, R06AD, R06AA02, R06AX02
Antipsychotics	Antipsychotics	N05A

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Excluded PIMs from Wallerstedt et al.

Drug name	ATC	Reason
Aprepitant	A04AD12	First choice treatment as antiemetic during some types of chemotherapy
Nortriptyline	N06AA10	First choice treatment in elderly if treated with TCA.
Opioids in combination with antispasmodics	N02AG	Not available in the Netherlands
Thiopropazate	N05AB05	Not available in the Netherlands
Expectorants combinations (cough)	R05CA10	Not available in the Netherlands
Prochlorperazine	N05AB04	Not available in the Netherlands

APPENDIX 2. Top 10 drug classes dispensed more at baseline among control patients than among MDD patients.

ATC-2 class	MDD patients n = 8121	Control patients n = 8121	p-value
S01 – Ophthalmologicals	14%	20%	**< 0.001**
C10 – Lipid modifying agents	33%	36%	**< 0.001**
A02 – Drugs for acid related disorders	32%	34%	**< 0.001**
C09 – Agents acting on the renin–angiotensin system	37%	39%	**0.009**
C08 – Calcium channel blockers	16%	18%	**0.001**
R03 – Drugs for obstructive airway diseases	14%	16%	**0.004**
D07 – Dermatological corticosteroids	7%	9%	**< 0.001**
J01 – Antibacterials for systemic use	12%	13%	**0.004**
R01 – Nasal preparations	2%	4%	**< 0.001**

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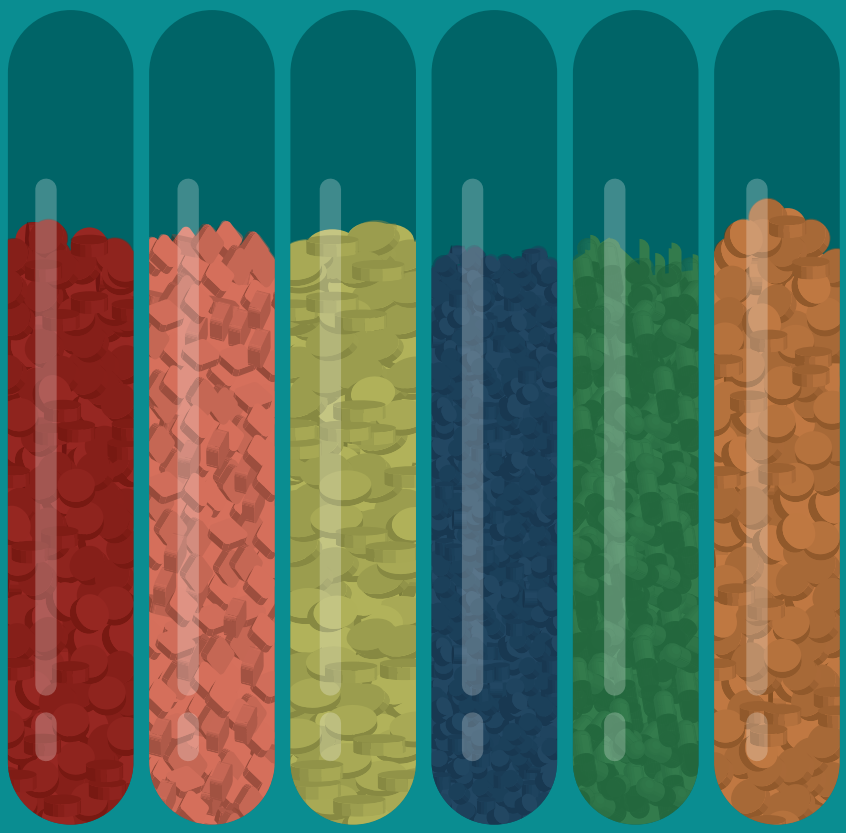

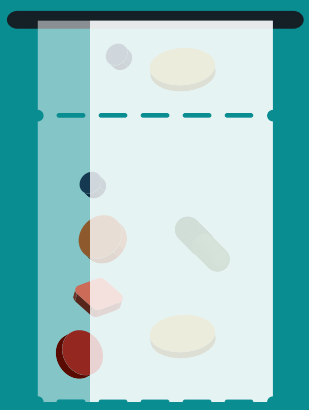

Chapter 4

Patients' experiences with multidose drug dispensing: a cross sectional study

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Abstract

Background: Automated multidose drug dispensing is used to support patients with their medication management. Though multidose drug dispensing systems are frequently used, little is known about patients' experiences with automated multidose drug dispensing (MDD) systems.

Objective: To explore patients' experiences with the initiation and use of MDD systems.

Setting A survey was carried out with patients using MDD systems through three community pharmacies.

Method: A semi-structured interview protocol was designed based on existing literature and a pilot study.

Main outcome measures: The main outcome measures were (1) patients' experiences with initiating multidose drug dispensing systems and (2) patients' experienced advantages and disadvantages of MDD systems.

Results: The start of multidose drug dispensing was discussed with 76% of the patients (n = 62). Ninety percent of patients expressed the opinion that the MDD system supported them with their medication management. Sixty patients reported 110 advantages, which can be organized into the following categories: improved medication adherence and medication safety (59%); patient's convenience (40%); and other (1%). Sixty-nine percent of patients reported no disadvantages, 24% had problems opening the bags or outer packaging and 13% had problems with the legibility of the printed text on the bag.

Conclusion: In concordance with the Dutch guideline, patients are generally involved in the decision to initiate an MDD system. Patients are very satisfied using the system and report multiple advantages. MDD systems may be further improved by simplifying the manual opening of the bags and improving the legibility of the text on the bags.

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Introduction

Despite the extensive research and attention of healthcare providers, patients' non-adherence to prescribed medication regimens remains a significant issue in healthcare.[1] Non-adherence can be divided in intentional and unintentional non-adherence.[2] Intentional non-adherent patients deliberately decide not to adhere to their drug therapy. Interventions that target intentional non-adherence focus on the patient's perceptions on medication.[2] Unintentional non-adherent patients are willing but unconsciously fail to adhere to their drug therapy. The capacity to adhere to the medication regimen may be diminished by a wide variety of reasons (e.g., a decline in cognitive function, polypharmacy, a change in appearance of outer packaging, or impaired manual dexterity).[3-5] Especially for unintentional non-adherence, the use of dosing aids such as multi-compartment compliance aids (MCAs) or automated multidose drug dispensing (MDD) systems can be an option.[6]

In the Netherlands, MDD systems are the preferred type of dosing aid, and the number of MDD users is rapidly increasing.[7] In the Netherlands, approximately 12% of patients aged ≥ 65 years use an MDD system.[8] In MDD systems, all solid medication intended for one dosing moment (e.g., capsules and tablets) is automatically packed in plastic disposable bags. Patient identification, content and designated time of intake is printed on the bags.[9,10] MDD systems are generally dispensed for a period of one to three weeks.

The Dutch guideline for patients using multi-compartment dosing aids recommends that patients who have difficulty adhering to their dosing regimens be primarily supported by simplification of complex dosing regimens, automatic refills of chronic medication or written dosing schemes.[7] If these options fail, an MDD system can be initiated. Shared decision making during this process is emphasised.

Little is known about patients' experiences and satisfaction with dosing aid. A small qualitative study of 15 users of various forms of dosing aids in the United Kingdom revealed that patients have divergent opinions.[11] Some experienced the use of a dosing aid as a supportive tool that helped them remain independent, while others perceived a loss of independence. Remarkably, patients stated that the initiation of the dosing aid was rarely discussed with them. These divergent results were supported by a second qualitative study among patients who lived in very sheltered housing in Scotland.[5] Patients' opinions differed regarding shared decision making, independence, medication knowledge and their confidence in managing their medication. Corresponding results were found in a survey among users of MCA admitted to a medical ward.[12] However, contrasting results were found in a questionnaire study that focused on patients'

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experiences with MDD systems.[13] Most patients were very satisfied using an MDD system. Though MDD systems are used extensively in the Netherlands, these patients' experiences with MDD systems are not well understood.

Aim of the study

The aim of this study was to explore patients' experiences with the initiation and use of MDD systems.

Ethics approval

In accordance with the Dutch Medical Research Involving Human Subjects Act, no formal ethical approval was needed to conduct this study. Patients gave written informed consent before the interview was conducted. In order to protect the patients' privacy, only age and gender were documented.

Method

Study design

This was a cross-sectional study between February and April 2016 among MDD users from three community pharmacies in the Netherlands. Patients were interviewed using a structured interview protocol (see Appendix 1). The interview focused on the patient's experiences with MDD systems. The initial version of the interview protocol (drafted by BM and SB) contained all questions from earlier studies which explored the patients' experiences and attitudes of MCAs or MDD systems.[11-13] Next, duplicate questions and questions not related to the use of the MDD systems were deleted. Closed-ended questions about specific advantages or disadvantages of MDD systems were replaced by open-ended questions on the advantages or disadvantages of an MDD system. Subsequently, the interview protocol was supplemented with questions derived from the recommendations from the Dutch guideline for patients using multi-compartment dosing aids.[7] HFK and MB commented on the drafted interview protocol. Based on the comments, the protocol was adjusted and tested in a small pilot among five patients. After the pilot, the protocol was once more adjusted. Ambiguous questions were altered and clarified. The final interview protocol contained both open-ended and closed questions.

Patients

The patients' community pharmacist first screened all users of MDD systems on inclusion and exclusion criteria. Patients over 18 years of age who received their drugs via an MDD

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system were eligible for inclusion. Patients with known severe cognitive impairment, who received palliative care or home care responsible for the administration of their medication, were excluded from participation. An independent researcher (SB) was temporarily seconded in the community pharmacy and invited patients to participate by telephone from their community pharmacy. If interested in study participation, patients received written study information. For the interview, patients were visited at home and before the start of the interview written informed consent was obtained. During the interview answers were written down by the independent researcher (SB). No audio recording was performed. Patients did not receive any payment or incentive for their participation and individual results were not shared with employees of the community pharmacy.

Sample size

The study was conducted in three average sized community pharmacies. We estimated that a total number of 405 patients would be eligible for inclusion. For a representative sample with an alfa of 10% and a power of 90%, 59 patients were needed.

Data coding and analysis

Answers from the five patients in the pilot phase were excluded from the analysis. Answers to open-ended questions were coded and assigned by two researchers (SB and BM). Discrepancies in coding were addressed in a consensus meeting. All data were analysed using statistical software (SPSS version 23.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were used for basic characteristics. Normally distributed data are presented with means and standard deviations (SD). For non-normally distributed data, median scores with the interquartile range (IQR) are presented. Answers to all questions are presented with absolute numbers and percentages.

Results

One hundred forty-seven patients were invited to participate, of which 62 (42%) gave informed consent. Patient characteristics are shown in Table 1. Median age was 79.5 and 57% (n=35) was female. The mean time per interview was 20 minutes (SD = 8). Patients indicated that pharmacists most often initiated the MDD system (22.6%, n=14), followed by the GP (14.5%, n=9) and the patient's family (14.5%, n=9). Home care (12.9%, n=8), the patient (6.5%, n=4) and a medical specialist (4.8%, n=3) also initiated MDD systems. 24.2% (n=15) of the patients could not remember who had initiated their MDD systems.

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TABLE 1: Characteristics of the included patients

Patient characteristics (n=62)	
Female; *n (%)*	35 (57%)
Age; *median (IQR)*	79.5 (74 – 85)
Years MDD system in use; *median (IQR)*	1.7 (0.5 – 4.1)
Number of drugs dispensed via MDD system; *mean (SD)*	7.8 (2.4)
Number of manually dispensed drugs; *median (IQR)*	4 (1 – 5)

Abbreviations: n = number; IQR = interquartile range; MDD = multidose drug dispensing; SD = standard deviation

TABLE 2: The reported advantages addressed to three domains and reported disadvantages

Domain	**Advantages**	**n= 110 (100%)**
Medication safety and adherence	I don't make mistakes with my medication anymore	44 (40%)
	It helps me not to forget to take my medication	15 (14%)
	I have a better overview over my medication	6 (5%)
Patient's convenience	I don't have to sort my medication anymore	15 (14%)
	The medication can easily be taken on an excursion or holiday	12 (11%)
	The medication is automatically prescribed and dispensed	10 (9%)
	The medication is periodically delivered at home	3 (3%)
	I spent less time taking my medication	2 (2%)
	I need less space to store my medication	1 (1%)
	The bags are more easy to open compared to blisters	1 (1%)
Other	There is less waste from packaging	1 (1%)
	Disadvantages	**37 (100%)**
	I have problems opening the outer packaging or pouches	15 (41%)
	I can't read the printed text on the pouches	8 (22%)
	It's difficult to identify the medication	5 (14%)
	It's difficult that not all medication is dispensed via the MDD system	3 (8%)
	Medication is only dispensed for a short period of time	2 (5%)
	The home delivery of the medication can be a problem	1 (3%)
	There is more waste from packaging	1 (3%)
	The MDD system contains generic medication	1 (3%)
	The MDD system contained medication that shouldn't be in the MDD system	1 (3%)

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The start of an MDD system was discussed with 76% (n=47) of the patients. MDD systems were initiated because the patient had a decreased medication management capacity (50% n=31), patient convenience (19%, n=12), forgetfulness (15%, n=9), practical problems related to the opening of the inner or outer packaging of medication (3%, n=2) and to anticipate on further decline of the patient's health (3%, n=2). Ten percent (n = 6) of the patients did not remember the reason for the initiation of the MDD system. Ninety percent (n=56) of patients were of the opinion that the MDD system supported them with their medication use, and 76% (n=47) indicated that the MDD system had improved their medication management. The median satisfaction rate for the use of an MDD system was 8 (IQR; 8 – 9) on a scale of 1–10 (1 extremely unsatisfied and 10 extremely satisfied). Two patients rated the use of an MDD system a 5, and none of the patients preferred to return to manual dispensing.

In total, 60 (97%) patients reported 110 advantages, and 2 patients (3%) reported no advantages. Most advantages were classified under the domain medication safety and adherence (59%, n=65) (see Table 2). Thirty-seven disadvantages were reported by 19 (31%) patients, and 43 patients (69%) reported no disadvantages. Most frequently reported disadvantages concerned difficulties with the opening of MDD systems (41%, n=15).

Discussion

For most patients, MDD systems were initiated after shared decision making. Patients were very satisfied with the use of MDD systems and expressed the belief that the system supported and improved their ability to use medication appropriately. However, disadvantages were also reported. These included difficulties opening the packaging and legibility of the printed text on the bags.

The divergent results found in the studies conducted in the United Kingdom and Scotland were not replicated in the present study.[5,11,12] In our study, patients were generally involved in the decision to initiate an MDD system and patient satisfaction with MDD systems was found to be high. Our results were more consistent with the results found by Bardage et al. among users of MDD systems in Sweden.[13] A direct comparison with Nunney et al. and Stewart et al. is difficult as, due to the qualitative study design, absolute numbers and percentages are lacking. In addition, Nunney et al. and Stewart et al. included residents who lived in (very) sheltered housing in contrast to our study where patients lived in the community without home care. However, in accordance with the both studies, the importance of the recommendation only to

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initiate an MDD system after a shared decision became again apparent in our study. The two patients who rated the use of an MDD system with a 5 were not consulted before the initiation. This emphasises the importance of involving the patient in the decision to initiate an MDD system.

Besides the improved medication adherence, the use of MDD systems has also some drawbacks. The patient's medication knowledge seems to diminish, not all the patient's medication can be dispensed via MDD systems and dispensing medication via an MDD system is more costly compared to manual dispensing. In addition, there are concerns about the drug stability of medication outside its original packaging.[14] If other interventions fail or are not appropriate (e.g., simplification of the drug medication regimen, the use of drug reminder charts, or the use of reminder alarms), an MDD system can be initiated. In half of the patients, an MDD system was initiated because the patient had a decreased medication management capacity. Patients with a decreased medication management capacity are willing to adhere but unconsciously fail because of a wide variety of reasons.[3] For these patients the initiation of an MDD system can be seen as appropriate.

However, also one quarter of the patients indicated that the initiation of an MDD system did not improve their medication management. This raises the question of why these patients were using an MDD system. When initiating dosing aids, it's advised to perform an individualized suitability assessment before the initiation of dosing aid.[7,14,15] Ideally, an intervention is used in which the patient continues to receive the medication via original packaging to maintain the patient's self-efficacy.[7,14,15] Our findings were in line with a different study among patients who were about to start with an MDD system in which 30% of the patients did not have a decreased medication management capacity.[3] No improvement can be expected among these patients. In the Netherlands, the use of MDD systems is reimbursed by health insurance and is about five times more expensive than manual dispensing. Initiating an MDD system solely for convenience is, therefore, inappropriate. For instance, one frequently cited advantage of MDDs—that medication can be easily taken on an excursion—can also be conferred with the use of a small pillbox. Therefore, other possible solutions must be explored before an MDD system is initiated.

Similar disadvantages to those found in previous studies were reported. Approximately 25% of the MDD users experienced difficulties with opening of the MDD system, though innovations like die-punched tear-lines have been introduced in the past years. These practical problems are not specific to MDD users, as can be concluded from the fact that similar percentages are also found among older adults who use original

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packaging.[4,16] However, the introduction of an MDD system has been described as a strategy to overcome these practical problems.[11,13] Whether the introduction of an MDD system solves these issues in reality remains unclear, as multiple patients continued to experience difficulties opening the MDD system. Especially patients with a reduced manual dexterity or reduced vision are prone to encounter problems regarding the packaging of their medication. On the other hand, there was one patient who described the opening of the MDD system as an advantage. It can be concluded that the MDD system's success as a solution depends on the individual patient's situation. When the decision is made to start an MDD system, patients' experiences must also be periodically evaluated, as their health status is expected to decline over time.[3] In general, the user friendliness of MMD systems might be improved with additional strategies which are targeted on patients with a reduced manual dexterity.

This study had several strengths. First, interviews were conducted by an independent interviewer at the patients' homes. This interviewer was an independent research associate unconnected to the community pharmacy. In this way, the risk of eliciting merely socially desirable answers was minimized. Second, this study explored the patients' experiences with both the initiation and continued use of MDD systems. Third, only patients who were responsible for their own medication management were included. Among these patients, MDD systems are intended to improve the patient's medication management. However, as earlier discussed, not all patients experienced an improvement in their medication management.

This study also had some potential limitations. First, patients were recruited on a voluntary basis, which might have introduced selection bias. Patients who were satisfied with the use of an MDD system might have been more willing to participate. Consequently, those with negative experiences with MDD systems might be underrepresented. In theory, patients who use an MDD system longer are more satisfied, but no correlation between the number of years patients used an MDD system and their satisfaction was found. That said, unsatisfied patients who had already returned to manual dispensing were not included in this study. Patients rarely return to manual dispensing in practice. Second, our study was designed as a structured interview with no room for in-depth questioning. The results show that most patients are satisfied but this does not account for all patients. To explore more in-depth the experiences and attitudes of the unsatisfied patients a qualitative study should be performed. Third, patients who received professional home care for the administration of the medication were excluded from participation. This group of patients might be especially likely to encounter problems with the use of MDD systems. However, these patients are supported with their medication use by home care workers who are trained and familiar with MDD systems. At last, the study was performed

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in only three community pharmacies all located in an urban area. All three pharmacies indicated to adhere to the Dutch guideline. Three pharmacies is a relatively low number of participating pharmacies. Possibly, results from more different pharmacies located in rural areas or who don't adhere to the Dutch guideline might differ.

Conclusion

Patients are generally involved in the decision to initiate an MDD system, however, there is still room for improvement. For most patients, the use of an MDD system seems appropriate, but there are also patients in who the use of an MDD system might be questionable. Patients are very satisfied using the system and report multiple advantages. MDD systems may be further improved by simplifying the manual opening of the bags and improving the legibility of the text on the bags. In order to be able to generalize the found results for all MDD users, results must be repeated with patients from different pharmacies.

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Conflicts of Interest

B. Mertens received an unconditional grant for a PhD project to multidose drug dispensing to conduct this research. The other authors declare no conflict of interest relevant to this study.

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Appendix 1: Survey for patients' experiences with MDD systems

The start of an MDD system

1. Who took the first initiative to start an MDD system?

   ☐ General Practitioner
   ☐ Community pharmacy
   ☐ Home-care
   ☐ Relative or friend
   ☐ Myself
   ☐ Different, namely:

2. Can you recall what the reason for the initiation of the MDD system?

_____

_____

3. Has the start of an MDD system been discussed with you?

   ☐ Yes
   ☐ No

4. What did you think of the idea to start using an MDD system?

_____

_____

5. On a scale of 1-10, how would you rate the use of an MDD system? :

The use of an MDD system

6. Can you describe how you open the plastic bags?

_____

_____

7. Do you experience troubles when opening the bags?

_____

_____

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8. Do you read the information on the bags?

   ☐ Always
   ☐ Sometimes
   ☐ Never

9. Do you experience problems reading the bags?

   ☐ Yes
   ☐ No

10. Can you describe how you take your drugs?

_____

_____

11. What is/are advantage(s) for you of receiving your drugs via an MDD system?

_____

_____

12. What is/are disadvantage(s) for you of receiving your drugs via an MDD system?

_____

_____

13. Would you prefer to return to manually dispensing?

   ☐ Yes
   ☐ No

14. Has the start of an MDD system improved your medication management?

   ☐ Yes
   ☐ No

15. Do you feel that an MDD system supports your medication management?

   ☐ Yes
   ☐ No

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Information provision

16. At which moment was explained how to use an MDD system?

    ☐ Before or at the start of the MDD system
    ☐ A few weeks after the start of the MDD system
    ☐ Never
    ☐ At a different moment, namely:

17. Would you like to receive more information about the use of an MDD system?

    ☐ Yes
    ☐ No

18. If yes, on which specific topic would you like to receive more information?

_____

_____

19. Do you always receive a new information leaflet when you start with a new drug?

    ☐ Yes
    ☐ No

20. If yes, what do you do with a new patient information leaflet?

_____

_____

21. Would you want to receive new patient information leaflets of the drugs in use on a yearly basis?

    ☐ Yes
    ☐ No

22. Can you show me where you store the information about the drugs you use?

    ☐ Is available and up to date
    ☐ Is available but not up to date
    ☐ Not available

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Drug changes

23. Does it happen that the appearance of drug in use changes?

    ☐ Yes
    ☐ No

24. If yes, can the change in appearance be a problem?

    ☐ Yes
    ☐ No

25. If yes, can you describe what is difficult for you when the appearance of a drug in use changes?

_____

_____

26. Does the community pharmacy inform you when the outer appearance of a drug changes?

    ☐ Yes
    ☐ No

27. If yes, in which way does the community pharmacy inform you?

_____

_____

28. If no, would you like to be informed about a drug change?

_____

_____

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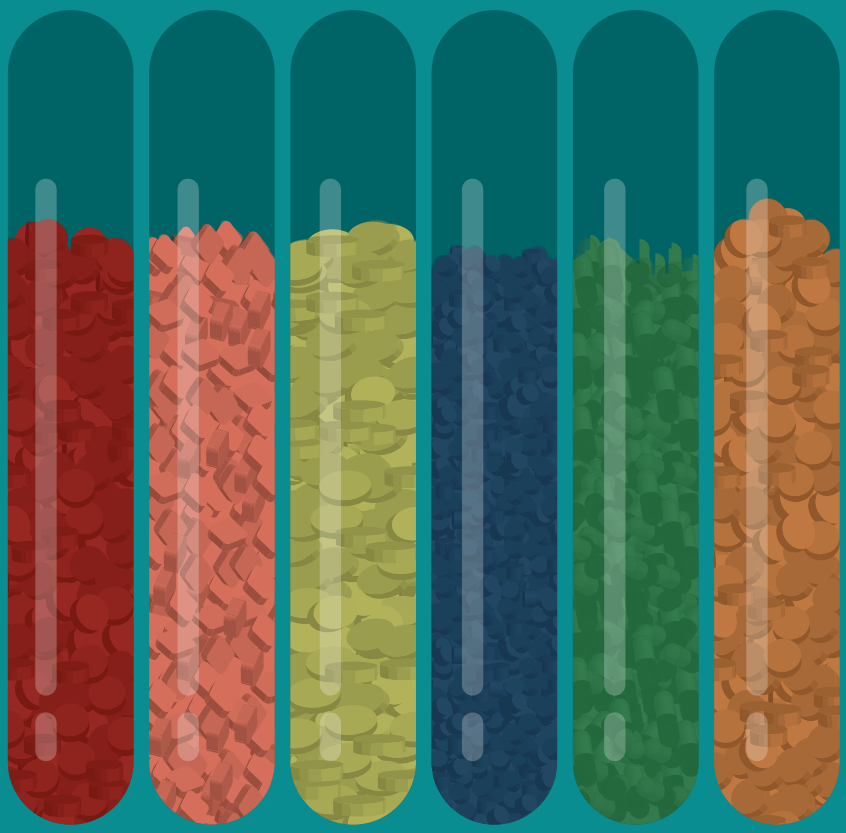

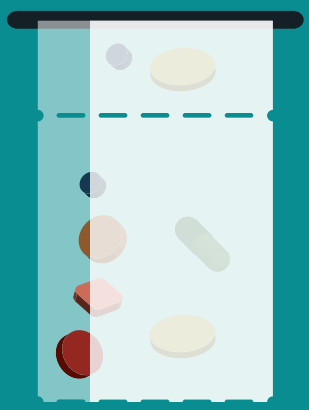

Chapter 5

Immediate or deferred adjustment of drug regimens in multidose drug dispensing systems

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Abstract

Background: Automated multidose drug dispensing (MDD) is used to help patients take their medicines appropriately. Little is known about medication regimen changes within these MDD systems and how they are effectuated by the community pharmacist. Immediate manual adjustments of the MDD system could introduce dispensing errors. MDD guidelines therefore recommend to effectuate medication regimen changes until the moment a new MDD system is ordered.

Objective: The aim of this study was to investigate the frequency, type, procedure followed, immediate necessity, and time taken to effectuate MDD adjustments.

Methods: This was a cross-sectional study in eight community pharmacies in the Netherlands. All adjustments to MDD systems were systematically documented for three weeks by the community pharmacist.

Results: Overall, 261 MDD adjustments involving 364 medication changes were documented in 250 patients: 127 (35%) medication changes involved the addition of new medication, 124 (34%) a change in dosage, and 95 (26%) medication discontinuation. Of the MDD adjustments, 135 (52%) were effectuated immediately: 81 (31%) by adjusting the MDD system manually, 49 (19%) by temporarily dispensing the medication separately from the MDD system, and 5 (2%) by ordering a new MDD system. Pharmacists considered that 36 (27%) of the immediate MDD adjustments could have been deferred until the next MDD system was produced. Immediate adjustment took significantly longer than deferred adjustment ($p < 0.001$).

Conclusions: This study shows that in patients using MDD systems, over half of the medication regimen changes are adjusted immediately. The necessity of these immediate changes should be critically evaluated.

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Introduction

In line with the number of patients on polypharmacy, the number of users of dosing aids has increased rapidly over the past years in the Netherlands.[1] Dosing aids can support patients with their medicine use, but there are also concerns about the prevalence of suboptimal drug treatment, a lower number of medication regimen changes among patients using dosing aids, and rigidity of dosing aids in immediate medication regimen changes.[2-12]

In the Netherlands, automated multidose drug dispensing (MDD) systems are predominately used as dosing aid.[13] In MDD systems, all oral solid medicines are automatically packed in disposable plastic bags, each containing the medicines to be taken on a given day. The disposable bags are labelled with patient data, content, date, and time of intake.[9] Because MDD systems are electronically packed, dispensing error rates are lower compared to manual filled dosing aids.[14,15]

In general, MDD systems are prepared by a specialized MDD supplier, based on prescription files forwarded from the pharmacy information system. Completed MDD systems, generally with medication for one week, are returned to the pharmacy for delivery to the patient.[9] The time between the between the order and delivery of MDD systems can take up to 5 days, depending on contractual agreements.

The Dutch guideline for dosing aids recommends that changes to the medicines in MDD systems are deferred until the next MDD system is due to be ordered, to lower the risk of dispensing errors.[13-16] However, this can delay the introduction of a new medicine by several days to more than a week. If immediate adjustment is necessary, technicians need to adjust the MDD system manually. This is time consuming and may introduce medication errors, as the proportion of errors is higher after manual adjustments compared to automated adjustments.[14,15] In the case of the addition of a new medicine or an increase in dosage, the new medication can temporarily be dispensed separately from the MDD system. However, separate dispensing can be confusing for patients who have lost the capacity to manage their medication.[17,18] A last option is the order of a new and adjusted MDD system. Completely replacing an MDD system takes a day and has additional costs. The different procedures thus all have their advantages and disadvantages. The pharmacists is responsible for the clinical risk management and final authorization and must weigh these pros and cons of immediate or deferred adjustment for every individual patient. When patients are unable to physically visit the pharmacy, couriers are available for home delivery. Despite the extensive use of MDD

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systems, little is known about how changes are made to MDD systems. The aim of this study was therefore to examine the frequency, type, followed procedure, immediate necessity, and time needed to effect changes to the medication in MDD systems.

Methods

Setting

This was a cross-sectional study which investigated the adjustments of medicines dispensed via automated MDD system in eight community pharmacies in the Netherlands. The community pharmacies participated on a voluntary basis in a pharmacy practice research course. All participating pharmacies were independent pharmacies and were located in both urban and rural areas.

Data collection

During three randomly assigned weeks, pharmacists documented all changes to medicines dispensed via an MDD system and how these changes were effectuated. A standardized electronic registration form using Survalyzer software was drafted with the help of the participating community pharmacists and tested in a pilot study. Data collection took place in February and March 2015. Besides the medication changes, basic characteristics about the total number of MDD users per pharmacy, and amount of medicines dispensed via MDD systems were collected.

Documentation of MDD adjustment

The following data were documented: age, gender, prescriber, type of medication changes (start, stop, dosage adjustment, other), medicines involved, procedure followed to effectuate the medication change, perceived necessity of the immediacy of each MDD adjustment, and time taken by pharmacy staff to effectuate the medication change. The perceived necessity was self-reported by the pharmacist and could be answered with yes or no. As it's not common to communicate the reason of medication changes on the prescriptions, pharmacists could consult the patient or prescriber about the reason for the medication change. A free text field was available for additional remarks. Only electronic prescriptions, sometimes presented by the patient were accepted for a medication change.

Each MDD adjustment could involve multiple medication changes (e.g., the addition of one medicine and the discontinuation of a second). Four types of medication changes were registered: (1) addition of a new medicine, (2) discontinuation of a medicine,

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(3) dose adjustment, (4) other. The procedure to effectuate the MDD adjustment was predefined as (1) immediate manual adjustment of the MDD system in use, (2) dispensing medication separately from the MDD system, (3) production of a new adjusted MDD system, (4) deferred adjustment until the start of the new MDD system. Options one to three were considered immediate adjustments. The time taken to effectuate the change was estimated by the individual staff members (pharmacist, pharmacist technician, and courier). Pharmacists received a study protocol with instructions and attended a joint meeting about the study.

Ethics and Confidentiality

According to the Dutch Medical Research Act Involving Human Subjects, no formal ethical approval was required for this observational study. The research protocol was reviewed by the Institutional Review Board of the Utrecht Pharmacy Panel for Education and Research (UPPER), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University. In order to protect patients' privacy, only age and gender were recorded.

Statistical analyses

All data were analysed using statistical software (SPSS version 23.0; SPSS Inc., Chicago, IL, USA). Medicines were classified according to the Anatomical Therapeutic Chemical (ATC) WHO Classification System level-2 and aggregated on therapeutic use. Descriptive statistics were used for basic characteristics, type, and procedure of MDD adjustment. Mean data ± standard deviation are reported, unless indicated otherwise. Pearson chi-squared tests were applied for categorical variables. Independent sample t-test was applied for continuous variables. Binary logistic regression with immediate or deferred adjustment as dependent variable was performed with adjustment for age, prescriber, one or more medication changes involved (binomial), and type of medication change. The results have been tested for normality. Differences in time taken were calculated using one-way Anova. If significant outcomes were obtained, a Dunnett's post-hoc test with deferred adjustment as reference group was performed. The median time for the order of a new extra MDD was tested using Mann-Whitney U test.

Results

Characteristics

There were 273 ± 138 MDD users per pharmacy (range 61-414), with 6.2 ± 0.7 medicines per MDD user. A total of 261 MDD adjustments were completely documented and

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involved 250 patients (median age 76 years, interquartile range 60-83) and 1.4 ± 0.9 medication changes per MDD adjustment. Five MDD adjustments were incomplete and discarded. The general practitioner (GP) initiated 138 (53%) MDD adjustments. 123 MDD adjustments were initiated by a variety of medical specialists. Psychiatrist (20%), cardiologists (16%) and internists (14%) were the three most frequent initiators among the medical specialists.

TABLE 1: The procedures followed to effectuate the MDD adjustment and the pharmacist' opinion about the necessity to effectuate the MDD adjustments immediately.

		Necessity of immediate change	
	Number of MDD adjustments % (n)	**Yes % (n)**	**No % (n)**
Immediate manual adjustment	31 (81)	70 (62)	30 (19)
Temporarily separate from MDD system	19 (49)	67 (33)	34 (16)
New extra MDD system ordered	2 (5)	80 (4)	20 (1)
Deferred until new MDD system	48 (126)	2 (3)	98 (123)
Total	**100 (261)**	**39 (102)**	**61 (159)**

Procedure

Of the MDD adjustments, 135 (52%) were effectuated immediately (options 1 to 3 as shown in Table 1). Differences were seen between the participating pharmacies in the procedures used to effectuate medication regimen changes (Appendix 1). Pharmacists who had a relatively high percentage of deferred adjustment indicated to have agreements with GPs about medication regimen changes among patients using an MDD system. In the opinion of the participating community pharmacists, 36 (27%) of all these adjustments could have been deferred and 3 (2%) of the deferred adjustments should have been made immediately.

MDD adjustments instigated by medical specialists were more likely to be effectuated immediately (adjusted OR 2.04; CI95% 1.16–3.59) than MDD adjustments instigated by GPs (adjusted for age and number of drugs). MDD adjustments involving more than one medicine were more likely to be effectuated immediately (adjusted OR 1.98; CI95% 1.04–3.77) than MDD adjustments involving one medicine (adjusted for age and prescriber).

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TABLE 2: Type of medication changes and moment of effectuation

Type of medication changes	Number of medication changes % (n)	Immediate adjusted % (n)	Deferred until new MDD % (n)	p-value *
Addition of new medicine	35 (127)	59 (75)	41 (52)	0.700
Discontinuation of a medicine	26 (95)	67 (64)	33 (31)	0.026
Dosage change	34 (123)	54 (67)	47 (56)	0.374
Addition of previous separate dispensed medicines	4 (14)	14 (2)	86 (12)	0.001
Change in time of intake	1 (3)	0 (0)	100 (3)	
Extra provision of lost medicines	0 (1)	100 (1)	0 (0)	
Manual addition of medication temporarily not in stock at the MDD supplier	0 (1)	100 (1)	0 (0)	
Total	**100 (364)**	**58 (210)**	**42 (154)**	**0.003**

* Pearson X^2 test

Type of medication change

The most common medication changes (n=364) were the addition of a new medicine (35%) and dosage adjustment (34%) (Table 2). Medication changes that involved discontinuation of a medicine were effectuated immediately more often than they were deferred (p=0.03). In contrast, MDD adjustments classified as 'other' were more likely to be deferred until the new regular MDD system was prepared (p=0.001).

Medication classes involved

Changes involving cardiovascular medicines (adjusted OR 1.79; CI95% 1.10–2.93) and medicines used in diabetes (adjusted OR 2.95; CI95% 1.19–7.29) were effectuated immediately more often than they were deferred. In contrast, changes involving vitamins and minerals were predominately deferred (adjusted OR 0.39; CI95% 0.13–0.86) (Table 3). A detailed overview of all the medication classes involved (ATC-2 classification) is presented in appendix 2, together with the type of medication change and procedure used to effectuate the medication change.

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TABLE 3: Medication classes and procedure to effectuate medication changes with adjusted odds ratio.

Medication classes	**Immediate adjustments** (n=210)	**Deferred adjustments** (n=154)	**Adjusted OR *** (95% CI)
Cardiovascular medication	69% (92)	31% (41)	**1.79 (1.10 - 2.93)**
Psycho(ana)leptic medication	47% (25)	53% (28)	0.77 (0.39 - 1.52)
Other medication	56% (18)	44% (14)	0.47 (0.33 - 1.66)
Medication used in diabetes	68% (19)	32% (9)	**2.95 (1.19 – 7.29)**
Gastrointestinal medication	58% (14)	42% (13)	0.56 (0.24 – 1.31)
Vitamins and minerals	36% (9)	64% (16)	**0.39 (0.13 - 0.86)**
Antibiotics and corticosteroids	77% (17)	23% (5)	1.91 (0.65 - 5.65)
Antiepileptic and antiparkinson medication	50% (8)	50% (8)	1.21 (0.41 – 3.58)
Analgesics	29% (4)	71% (10)	0.38 (0.11 - 1.30)
Anti-rheumatics and anti-gout medication	29% (4)	71% (10)	0.33 (0.09 - 1.14)

OR: Odds Ratio
* adjusted for age, prescriber, number of medicines involved in medication changes and type of medication change. Statistically significant associations printed in bold

TABLE 4: Time taken per MDD adjustment for each staff member per procedure with deferred adjustment as reference group.

	Number of documented MDD adjustments (n)	**Pharmacist median time** (min + IQR)	**Pharmacist technician median time** (min + IQR)	**Home delivery median time** (min + IQR)
Immediate manual adjustment	81	2 (2) *	12 (8) *	0 (10) *
Temporarily separate from MDD system	49	1 (1)	10 (9) *	0 (1) *
New extra MDD system ordered	5	5 (21) ‡	22 (36)	0 (5) ‡
Deferred until new MDD system	126 (reference group)	1 (0)	4 (5)	0 (0)

MDD: multidose drug dispensing; min: minutes; IQR: interquartile range
* is significant with p value < 0.05 tested with Anova Dunnett's post-hoc test.
‡ is significant with p value < 0.05 tested with Mann-Whitney U test.

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Time taken

The total time needed to adjust an MDD system was in average 15.6 ±15.8 minutes (2.4 ± 3.7 minutes for the pharmacist, 11.1 ± 12.0 minutes for the pharmacy technician, and 2.2 ± 5.1 minutes for the home delivery courier). Immediate manual adjustment took pharmacy staff, especially technicians, longer than deferred adjustment ($p < 0.001$) (see Table 4).

Discussion

This study shows that half of the MDD adjustments were effectuated immediately, with the addition of medication and dosage changes being the most common reason for adjustment of MDD systems. Pharmacists were of the opinion that around half of these immediate medication regimen changes could be deferred adjusted. A reduction in immediate adjustments would result in improved dispensing efficacy as immediate adjustments took around twice the time compared to deferred adjustments.

About half of the medication changes were manually effectuated. This high percentage seems in contradiction with the recommendation of the Dutch MDD guideline to minimize manual adjustments in order to decrease the risk of dispensing errors.[13] Besides the risk of dispensing errors, manual adjustment is also labour intensive. The considerable differences in preferred procedure between the participating pharmacies suggest that it is possible to influence the procedure to adjust MDD systems. Reducing the number of immediate adjustments, may render community pharmacists additional time that can be invested in other pharmaceutical care activities from which patients can benefit.[19] Explicit agreements and timely communication between prescribers, patients, and pharmacists about the reason and acuteness of immediate MDD adjustments might decrease the number of immediate MDD adjustments.

According to the participating community pharmacists, approximately one quarter of the immediate adjustments could have been deferred. This is surprising considering that the medication regimen change were effectuated immediately by the pharmacist. The reason why pharmacists effectuated the medication change immediately, against estimation, was not documented for every medication change. In practice, it is the role of the technician to effectuate the medication change. Pharmacists are responsible for the clinical risk management and final authorization. Based on the free text clarifications that were given by the pharmacists, we conclude that practical arguments often

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influenced the choice between immediate or deferred adjustment (e.g., the patient is already expecting an immediate change, the prescriber cannot be reached or the pharmacy technician has already prepared an immediate change).

Opposite of the one quarter of immediate medication changes that could have been deferred, in 2% of the deferred adjustments pharmacists were of the opinion that the medication change should have been effectuated immediately. In these cases patients had already identified the medicines that were discontinued and had discarded these from the MDD system themselves. However, identification of the appropriate tablet can be difficult, especially if one bag contains multiple white round tablets. Leaving this difficult task as a responsibility of the patient, who uses an MDD system to support him with appropriate use of his medication, can introduce new risks.

Besides the high number of manual adjustments, a frequently chosen option was to dispense the newly prescribed or changed medication separately from the MDD system. The provision of medication separate from the used dosing aid could be confusing for patients with a limited medication management capacity.[17,18] Separate dispensing of newly prescribed medication might thus increase the risk of medication errors.[20] Therefore medication should only be dispensed separately from the automated MDD system, when the patient or an informal carer has an adequate medication management capacity. An exception are patients who receive help with medication administration from professional home-care workers. In these circumstances, the provision of separate medication is appropriate provided that the home-care worker is fully informed about the new situation.[13,20]

Replacement of the MDD system in use by a completely new MDD system is a convenient and safe method to effectuate medication regimen changes that involve multiple medication changes. However, only 2% of the MDD adjustments were effectuated by ordering a completely new MDD system. The additional costs for the order of a new MDD and the discarded medicines from the MDD system currently in use might deter pharmacists from using this option.

From a pharmacological perspective, medicines for primary or secondary prevention with long-term beneficial effects (e.g., antihypertensive, lipid modifying agents, or vitamins) seem candidates for deferred adjustment. In contrast, if a patient experiences discomfort (e.g., pain medication, antibiotics, or medication withdrawal because of adverse drug events) immediate adjustment of the MDD system is warranted. In this study, 44% of the immediate effectuated medication changes involved cardiovascular medication, while these are frequently used for their long-term effects. However, it is

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difficult to evaluate the necessity for immediate MDD adjustment if the indication is not available for the pharmacist. For example, metoprolol can be initiated for blood pressure regulation (immediate adjustment not necessary) but also for cardiac arrhythmia (immediate adjustment necessary). In order to be able to appraise the immediate necessity of an MDD adjustment, the pharmacist should be familiar with the reason for a medication change.

This was the first study that prospectively documented changes made to the medicines prescribed to users of MDD systems. Although MDD is used extensively, little has been described about the frequency and type of changes made to medicines dispensed via MDD. Sjöberg et al. reported that, of patients hospitalized for hip fracture, patients using MDD systems experienced fewer medication changes than patients receiving medicines via manually dispensed medicines after hospital discharge.[3] A cohort study by Wallerstedt et al. found an increased number of medicines in use, more potentially harmful medicines and fewer medication changes after the transition from manual dispensing to MDD.[5] In the current study, an average of 2.1 MDD adjustments per MDD user per year was found. Because of a lack of data on changes in manually dispensed medicines, no comparison could be made with users of manually dispensed medicines, or with data from other studies.

Besides the lack of data on manually dispensed medicines, the study had also some other potential limitations. First, only eight pharmacies participated in the study. The participating pharmacies, however, did differ in size and location (urban and rural community pharmacies). Second, because this was an observational study investigating the procedures followed by community pharmacists, the effect of deferred adjustments on clinical outcomes has not been assessed. As a consequence of the observational design of the study pharmacists received no explicit instructions on how to assess the immediate necessity of MDD adjustments. Whether clear instructions and explicit agreements between prescribers and pharmacists indeed can reduce the number of immediate adjustments must be elucidated in further research combined with the effect on clinical outcomes. Third, the number of days until the deferred adjustment was effectuated was unknown. Theoretically, this might be of influence on the pharmacist's decision to immediately adjust the MDD system. Last, the time needed to make adjustments was self-reported and not recorded by an independent observer. In the meeting before the study, the importance of accurate recording of the time was emphasized.

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Conclusion

Half of the adjustments made to MDD systems were effectuated immediately. Immediate effectuated medication regimen changes took twice the time compared to deferred adjustments. Deferred adjustment of changes to MDD systems is preferable when appropriate. Explicit agreements and timely communication between patients, prescribers, and community pharmacists about the necessity of immediate medication changes is therefore needed to improve dispensing efficiency.

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Compliance with ethical standards

According to the Dutch Medical Research Act Involving Human Subjects, no formal ethical approval was required for this observational study. The research protocol was reviewed by the Institutional Review Board of UPPER, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University.

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Conflicts of Interest

B. Mertens received an unconditional grant for a PhD project to multidose drug dispensing to conduct this research. The other authors declare no conflict of interest relevant to this study.

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APPENDIX 1: Procedure followed by individual pharmacies to effectuate drug regimen changes.

	Pharmacy (number of MDD users)								
	1 (414)	**2 (345)**	**3 (236)**	**4 (128)**	**5 (397)**	**6 (194)**	**7 (61)**	**8 (410)**	**Total (2185)**
1. Immediate manual adjustment	69% (25)	22% (7)	4% (1)	41% (11)	24% (11)	27% (14)	17% (2)	34% (10)	31% (81)
2. Temporarily separate from MDD system	6% (2)	38% (12)	14% (4)	22% (6)	20% (9)	18% (9)	0% (0)	24% (7)	19% (49)
3. New extra MDD system ordered	0% (0)	0% (0)	0% (0)	4% (1)	9% (4)	0% (0)	0% (0)	0% (0)	2% (5)
4. Deferred until new MDD system	25% (9)	41% (13)	82% (23)	33% (9)	48% (22)	55% (28)	83% (10)	41% (12)	48% (126)
Total	100% (36)	100% (32)	100% (28)	100% (27)	100% (46)	100% (51)	100% (12)	100% (29)	100% (261)

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APPENDIX 2: Individual medication classes on ATC-2 level, type of medication change and procedure used for medication change.

ATC classification system	Number of drugs involved (n=364)	Addition of new medication (n=127)	Discontinuation of medication (n=95)	Dose adjustment (n=123)	Other (n=19)	Immediate adjusted (n=210)	Deferred adjusted (n=154)	p-value *
Cardiovascular medication	**133**	**33% (44)**	**35% (47)**	**26% (35)**	**5% (7)**	**69% (92)**	**31% (41)**	**0.017**
B01 - Antithrombotic agents	17	29% (5)	53% (9)	12% (2)	6% (1)	65% (11)	35% (6)	
C01 - Cardiac therapy	9	11% (1)	33% (3)	33% (3)	22% (2)	78% (7)	22% (2)	
C03 - Diuretics	30	47% (14)	20% (6)	27% (8)	7% (2)	63% (19)	37% (11)	
C07 - Beta blocking agents	26	27% (7)	31% (8)	42% (11)	0% (0)	73% (19)	27% (7)	
C08 - Calcium channel blockers	19	42% (8)	47% (9)	11% (2)	0% (0)	79% (15)	21% (4)	
C09 - Agents acting on the renin-angiotensin system	18	33% (6)	33% (6)	33% (6)	0% (0)	83% (15)	17% (3)	
C10 - Lipid modifying agents	14	21% (3)	43% (6)	21% (3)	14% (2)	43% (6)	57% (8)	
Psycho(ana)leptic medication	**53**	**26% (14)**	**13% (7)**	**53% (28)**	**8% (4)**	**47% (25)**	**53% (28)**	**0.439**
N05 - Psycholeptics	36	22% (8)	11% (4)	56% (20)	11% (4)	56% (20)	44% (16)	
N06 - Psychoanaleptics	17	35% (6)	18% (3)	47% (8)	0% (0)	29% (5)	71% (12)	
Other medication	**32**	**44% (14)**	**31% (10)**	**19% (6)**	**6% (2)**	**56% (18)**	**44% (14)**	**0.546**
G03 - Sex hormones and modulators of the genital system	1	0% (0)	0% (0)	100% (1)	0% (0)	0% (0)	100% (1)	
G04 - Urologicals	8	63% (5)	25% (2)	13% (1)	0% (0)	63% (5)	37% (3)	
H03 - Thyroid therapy	1	0% (0)	0% (0)	100% (1)	0% (0)	100% (1)	0% (0)	
H05 - Calcium homeostasis	2	50% (1)	0% (0)	50% (1)	0% (0)	0% (0)	100% (2)	
L02 - Endocrine therapy	4	50% (2)	50% (2)	0% (0)	0% (0)	100% (4)	0% (0)	
N07 - Other nervous system medicines	2	50% (1)	50% (1)	0% (0)	0% (0)	50% (1)	50% (1)	
R03 - Medication for obstructive airway diseases	1	100% (1)	0% (0)	0% (0)	0% (0)	0% (0)	100% (1)	

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APPENDIX 2: Continued.

ATC classification system	Number of drugs involved (n=364)	Addition of new medication (n=127)	Discontinuation of medication (n=95)	Dose adjustment (n=123)	Other (n=19)	Immediate adjusted (n=210)	Deferred adjusted (n=154)	p-value *
R05 - Cough and cold preparations	2	50% (1)	50% (1)	0% (0)	0% (0)	50% (1)	50% (1)	
R06 - Antihistamines for systemic use	8	38% (3)	38% (3)	0% (0)	25% (2)	38% (3)	62% (5)	
V03 - All other therapeutic products	3	0% (0)	33% (1)	67% (2)	0% (0)	100% (3)	0% (0)	
Medication used in diabetes	**28**	**4% (1)**	**18% (5)**	**75% (21)**	**4% (1)**	**68% (19)**	**32% (9)**	**0.043**
A10 - medication used in diabetes	28	4% (1)	18% (5)	75% (21)	4% (1)	68% (19)	32% (9)	
Gastrointestinal medication	**27**	**41% (11)**	**26% (7)**	**22% (6)**	**11% (3)**	**58% (14)**	**42% (13)**	**0.272**
A02 - Medication for acid related disorders	23	48% (11)	22% (5)	17% (4)	13% (3)	52% (12)	48% (11)	
A03 - Medication for functional gastrointestinal disorders	1	0% (0)	100% (1)	0% (0)	0% (0)	100% (1)	0% (0)	
A06 - Medication for constipation	2	0% (0)	0% (0)	100% (2)	0% (0)	0% (0)	100% (2)	
A09 - Digestives, including enzymes	1	0% (0)	100% (1)	0% (0)	0% (0)	100% (1)	0% (0)	
Vitamins and minerals	**25**	**72% (18)**	**24% (6)**	**4% (1)**	**0% (0)**	**36% (9)**	**64% (16)**	**0.032**
A11 - Vitamins	11	91% (10)	0% (0)	9% (1)	0% (0)	22% (2)	78% (9)	
A12 - Mineral supplements	3	67% (2)	33% (1)	0% (0)	0% (0)	67% (2)	33% (1)	
B03 - Antianemic preparations	10	50% (5)	50% (5)	0% (0)	0% (0)	40% (4)	60% (6)	
Y -	1	100% (1)	0% (0)	0% (0)	0% (0)	100% (1)	0% (0)	
Antibiotics and corticosteroids	**22**	**64% (14)**	**5% (1)**	**32% (7)**	**0% (0)**	**77% (17)**	**23% (5)**	**0.823**
J01 - Antibacterials for systemic use	11	91% (10)	9% (1)	0% (0)	0% (0)	78% (9)	22% (2)	
H02 - Corticosteroids for systemic use	11	36% (4)	0% (0)	64% (7)	0% (0)	62% (8)	38% (3)	

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APPENDIX 2: Continued.

ATC classification system	Number of drugs involved (n=364)	Addition of new medication (n=127)	Discontinuation of medication (n=95)	Dose adjustment (n=123)	Other (n=19)	Immediate adjusted (n=210)	Deferred adjusted (n=154)	p-value *
Antiepileptic and antiparkinson medication	**16**	**13% (2)**	**25% (4)**	**56% (9)**	**6% (1)**	**50% (8)**	**50% (8)**	**0.524**
N03 - Antiepileptics	12	17% (2)	33% (4)	42% (5)	8% (1)	33% (4)	67% (8)	
N04 - Anti-parkinson medication	4	0% (0)	0% (0)	100% (4)	0% (0)	100% (4)	0% (0)	
Analgetic medication	**14**	**29% (4)**	**215 (3)**	**50% (7)**	**0% (0)**	**29% (4)**	**71% (10)**	**0.091**
N02 - Analgesics	9	22% (2)	22% (2)	56% (5)	0% (0)	33% (3)	67% (6)	
M01 - Anti-inflammatory and antirheumatic products	5	40% (2)	20% (1)	40% (2)	0% (0)	20% (1)	80% (4)	
Anti-rheumatics and antigout medication	**14**	**36% (5)**	**36% (5)**	**21% (3)**	**7% (1)**	**29% (4)**	**71% (10)**	**0.076**
L04 - Immunosuppressants	1	100% (1)	0% (0)	0% (0)	0% (0)	100% (1)	0% (0)	
M04 - Antigout preparations	4	25% (1)	0% (0)	75% (3)	0% (0)	25% (1)	75% (3)	
M05 - Medication for treatment of bone diseases	7	14% (1)	(5) 71%	0% (0)	14% (1)	14% (1)	86% (6)	
P01 - Antiprotozoals	2	100% (2)	0% (0)	0% (0)	0% (0)	50% (1)	50% (1)	

* adjusted for age, prescriber, number of medicines involved in medication change and type of medication change

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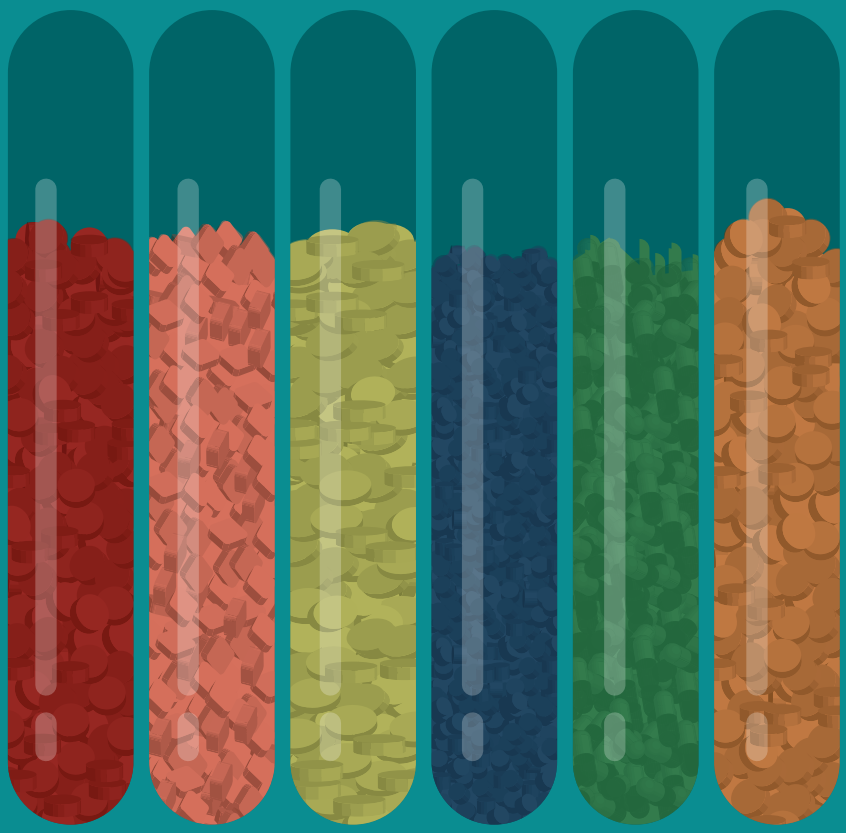

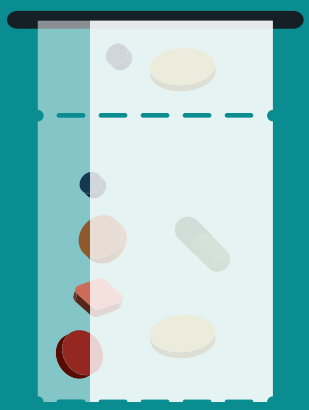

Chapter 6

The effect of dispensing vitamin K antagonists via a multidose drug dispensing system on the time in therapeutic range: study protocol of a randomised controlled trial

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Abstract

Background: A significant proportion of patients using vitamin K antagonists (VKAs) have a low quality of anticoagulation treatment expressed by a time in therapeutic range (TTR) < 65%. A low TTR may be due to non-adherence to the complex dosing regimens for the VKA. Dosing aids like multidose drug dispensing systems (MDD) may improve adherence and subsequently improve TTR in patients with a low TTR. This study will determine the effect of dispensing VKA via an MDD on the TTR in patients with a TTR < 65%.

Methods: A randomised controlled trial in 18 community pharmacies in the Netherlands. Patients in the intervention group receive VKA via an MDD system, whereas control patients receive manually dispensed VKA. The primary outcome is the change in TTR calculated conform the Rosendaal method. Secondary outcomes are: time under and above therapeutic range, the number of vitamin K prescriptions, mean number of INR measurements, change in mean vitamin K antagonist dose, and change in self-reported medication adherence. Primary outcomes will be assessed using a mixed-effects model.

Discussion: MDD systems are expected to improve medication adherence. However, little is known about the actual effect of MDD systems on health outcomes. This study will be able to provide more insight in the effect of MDD systems on medication adherence and is powered to translate improved adherence to patients' TTR, a very important parameter which expresses the quality of the anticoagulation therapy. Due to the nature of the intervention, patients are aware of group allocation. Beside adherence to vitamin k antagonists, the TTR can be affected by a wide variety of reasons from which we are unaware. These might influence final results.

Trial registration The trial is registered at the Dutch trial register (NTR5883). Registered at 30 May 2016.

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Background

Vitamin K antagonists (VKAs) are highly effective drugs to treat and prevent thromboembolism.[1,2] Despite the introduction of the non-vitamin K antagonist oral anticoagulants (NOACs), the VKAs phenprocoumon, acenocoumarol and warfarin are still prescribed extensively as antithrombotics. In 2015, 2,5% of the Dutch population used VKAs to prevent thromboembolism.[3] Monitoring of VKA therapy differs between countries but always consists of regular International Normalized Ratio (INR) assessment and adjustment of dosing regimens. From consecutive INR values, the time in therapeutic range (TTR) can be calculated using the Rosendaal method.[4] The TTR reflects the therapeutic quality of the anticoagulation treatment. A low TTR is associated with an increased risk of bleeding and thromboembolism.[5-7] In the Netherlands, monitoring is performed by specialized anticoagulation clinics. Despite intensive support from the anticoagulation clinics, around 20% of the patients have a TTR < 65% which is considered inadequate.[5,8]

A low TTR can be caused by a variety of reasons like comorbidities, co-medication, alcohol, genetics, food etc.[9,10] Another explanation is a reduced adherence to VKA, possibly caused by the complexity of the antithrombotic dosing regimens.[11] Especially community dwelling older patients frequently experience problems managing their medication due to several reasons including difficult dosing regimens, polypharmacy, cognitive dysfunction, and impaired manual dexterity.[12-14] Patients who lost their medication management capacity (MMC) may benefit from dosing aids. In the Netherlands, the majority of patients in need of dosing aids receive their drugs via multidose drug dispensing (MDD).[15] In MDD systems all oral solid drugs are automatically packed in disposable plastic sachets. These disposable sachets are labelled with patient data, content, date, and time of intake.[16] A Cochrane meta-analysis showed that dosing aids improved medication adherence, diastolic blood pressure and HbA1c levels.[17] In a cross-sectional study users of MDD systems reported to be adherent for 91% of their drugs compared to 58% for users of manually dispensed drugs.[16]

Not every drug is suitable for MDD due to practical packaging issues (e.g., sachets, liquids, eye drops, suppositories) or fluctuating dosing regimens like VKAs. These drugs remain generally manually dispensed beside the MDD system. This seems counter-intuitive as VKAs belong to the most complex drugs to manage. By dispensing the VKA via an MDD system, the adherence and consecutively the TTR can be improved. Therefore the aim of the study is to determine the effect of dispensing VKAs via MDD on the TTR in patients with a low quality of anticoagulation.

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Methods

Design and setting

This is a randomized controlled trial with two study groups (allocation ratio 1:1) in 18 community pharmacies located in the catchment area of the Leiden Anticoagulation Clinic. The study was designed conform the SPIRIT statement.[18] An overview of the study flow is given in Table 1.

TABLE 1: Study flow

TIMELINE	**All patients**	
t=-1 month	TTR assessment over past 6 months by the Leiden Anticoagulation Clinic	
t=0 months	Written informed consent Patient interview 1. Baseline characteristics 2. Mini-Cog 3. Medication Management capacity Completed by the patient 4. MARS 5. GFI 6. Beliefs about Medicines questionnaire	
	Intervention group (n=104)	**Control group (n=104)**
t=0 months	VKA is dispensed via an MDD system	Usual care
t=2-4 weeks	Evaluation of MDD conform pharmacist guideline.	Usual care
t=6 months	1. MARS for VKA 2. Data extraction: TTR data extraction from Leiden Anticoagulation Clinic. Dispensing record from community pharmacies 3. TTR assessment during study period 4. manual dispensing is offered	1. MARS for VKA 2. Data extraction: TTR data extraction from Leiden Anticoagulation Clinic. Dispensing record from community pharmacies 3. TTR assessment during study period 4. MDD is offered

Participants

Patients with a TTR < 65% in the 6 months before inclusion in the study are eligible to participate.[5] Every three months the Leiden Anticoagulation Clinic will generate a selection of eligible patients. Inclusion and exclusion criteria are shown in Table 2. To include patients with a higher probability of experiencing problems in managing their medication, patients have to be ≥ 65 years of age and use ≥ 5 chronic oral prescription

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drugs. As fluctuation of INR frequently occurs during the first 6 to 8 weeks of VKA use, and because baseline TTR was assessed over a period of 6 months, patients with VKA use shorter than 9 months are not eligible for inclusion.[7] To minimize loss to follow up, patients with an expected short duration of VKA treatment (e.g., first venous thrombosis) or with a short life expectancy are excluded from participation. Additional exclusion criteria are receiving home-care for help with administration of medication, current treatment administration of intravenous chemotherapy and self-management of VKA therapy.

Eligible patients are informed by postal mail by their community pharmacist. Within one week after the information letter patients are invited to participate by telephone.

TABLE 2: Inclusion and exclusion criteria

Inclusion criteria:	**Exclusion criteria:**
TTR < 65% over last 6 months	Patient self-management of VKA medication
≥ 65 years of age	Patient with recurrent chemotherapy
≥ 5 chronic oral drugs	Patient with short life expectancy (<6 months)
Lifelong indication for VKA	Patient receives home-care responsible for the administration of medication
	Patients with VKA distributed via an MDD system
	Vitamin-K antagonist use < 9 months

Sample size calculation

Based on historic data from the Leiden Anticoagulation Clinic, a standard deviation in TTR of 23% is used. A relevant clinical effect is defined as an absolute improvement in TTR of 10% between the intervention and control group (e.g., 70% vs 60%). To demonstrate an absolute difference in TTR of 10% for the primary outcome with an alfa of 0.05 and a power of 80%, a total number of 83 patients in both the intervention and the control group are needed. To compensate for loss to follow-up 25% extra patients will be included in both study groups which results in a total of 208 patients.

Recruitment

For formal written informed consent and an interview, patients are visited at home by their community pharmacist, a pharmacy technician or a research assistant. Based on historic data from the Leiden Anticoagulation Clinic approximately 1500 patients are eligible to participate in the study based on age and TTR. An average sized pharmacy

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has around 220 users of VKAs from which approximately 45 have a TTR < 65%. From these 45 patients, an average of 12 patients per pharmacy in 18 community pharmacies must be recruited to achieve the required 208 patients.

Intervention

Patients in the intervention group receive all chronic solid oral prescription drugs via an MDD system, including VKA. Patients in the control group receive VKA in original packaging. If patients in the control group received co-medication via an MDD system before randomisation, they continue to use all other drugs via an MDD. As a consequence four different groups emerge (1) intervention: start MDD including VKA, (2) intervention: addition VKA to MDD already in use, (3) control: continue manually dispensed drugs including VKA and (4) control: continue MDD and VKA manually dispensed.

To enable community pharmacies to distribute VKAs via an MDD system, dosing schemes are sent to both the patient and community pharmacy. Dosing schemes for patients who continue to use their VKA via manual dispensing are only sent to the patient. The shortest VKA dosing regimens are automatically extended by the anticoagulation clinic from 7 to 10 days, thereby enabling the community pharmacist to order or produce MDD systems.

Randomisation and blinding

Randomisation is stratified for patients already receiving co-medication via an MDD and patients using manually dispensed co-medication. Two randomisation sequences, both containing 208 numbers, are generated using SPSS (version 23.0, SPSS Inc., Chicago, IL, USA). After written informed consent, patients are randomised (1:1) by the main investigator (BM). Due to the nature of the intervention it is impossible to perform a double blind trial. Group allocation is not blinded for patients, pharmacists and investigators. The physicians of the Leiden Anticoagulation Clinic are unaware of the patient's study participation, but aware that the patient uses an MDD system. Data will be analysed by an independent statistician who will be blinded for group allocation.

Questionnaires

At the start of the study, patients are interviewed by the community pharmacist, pharmacist technician or research assistant. The interview was based of two questionnaires, the Mini-Cog and a self-developed questionnaire regarding the medication management capacity (MMC).[19] Additionally, patients are asked to complete the Beliefs about Medicines Questionnaire, Medication Adherence Report Scale and Groningen Frailty Indicator. [20-22]

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Beliefs about Medicines Questionnaire (BMQ)

The effect of the intervention might be influenced by patients' beliefs about their treatment. To explore the influence of the patients' beliefs on the effect of the intervention, the Beliefs about Medicines Questionnaire (BMQ) specific was conducted. The BMQ specific questionnaire consists of 10 questions on a five-point Likert scale (1=fully disagree, 2=disagree, 3=uncertain, 4=agree, 5=fully agree) that cover two domains (Appendix 1).[20] Five questions cover the patients' beliefs about the necessity of VKA treatment, the other five questions cover the patients' concerns about VKA treatment. Based on the BMQ, patients can be categorised in four different attitudinal groups; accepting (high necessity, low concerns), ambivalent (high necessity, high concerns), sceptical (low necessity, high concerns) and indifferent (low necessity, low concerns).

Medication Adherence Report Scale

Self-reported adherence is measured with the Medication Adherence Report Scale (MARS).[21] The MARS contains 5 statements on both intentional and unintentional non-adherence which can be scored on a five-point Likert scale (1=always, 2=often, 3=sometimes, 4=rarely and 5=never) (Appendix 2). The cut-off score of ≥ 23 was considered as adherent, because this was applied in a previous study in measuring adherence in MDD. [16] The MARS is repeated after six months.

Groningen Frailty Indicator

Frailty has been associated with a reduced TTR.[23] Therefore frailty is assessed with the Groningen Frailty Indicator (GFI), which is a validated tool and consists of 15 generic questions (Appendix 3). Each question can be scored with 0 or 1 point. Scores are dichotomised with a cut-off point of four or more classifying the patient as frail.

Mini-Cog

A decreased TTR has also been associated with decreased cognition.[24,25] Therefore cognition is assessed with the Mini-Cog. The Mini-cog is easier to apply compared to the Mini Mental State Examination (MMSE) but well correlated to MMSE score.[26] If scored between zero and two points, this suggests a possible cognitive impairment (Appendix 4).

Medication Management Capacity

Multiple instruments have been designed to determine the MMC.[27-29] In a previous study, an extensive questionnaire was designed to identify potential problems in the patient's medication management. This questionnaire was designed by combining

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questions from different medication management assessment tools supplemented with questions identified in a small pilot.[30,31] For the previous study, the questionnaire was abbreviated. From each of the four domains, the question that was most correlated with a reduced MMC was included in the new questionnaire. Two additional questions that we estimated to be important for the patient's MMC were also included. These six questions were supplemented with the patient's own estimation of his MMC and two questions that were related to the patient's home situation. (Appendix 5). Every question can be scored a 0 (no possible problem) or a 1 (possible problem), resulting in a score ranging from 0 to 9.

Fidelity to intervention

Community pharmacies were recruited during regional meetings where the study design was presented. Interested community pharmacies were visited by BM and received additional information about the study protocol. Finally, a joint kick-off meeting with the Leiden Anticoagulation Clinic and all participating community pharmacies was organised. After the start of the study community pharmacies received optional support from the investigators or a research assistant.

Outcomes

The primary outcome will be the difference in TTR between six months before the study and during the six month study period. The index date for the intervention is the first day VKA are dispensed via MDD. The index date for control patients is the date of the interview.

Secondary outcomes

The average number of vitamin K doses prescribed for uncontrolled INR are assessed together with the mean number of INR measurements at the Leiden Anticoagulation Clinic. To determine the difference in self-reported adherence the MARS scores of VKA are assessed at t=0 and after six months. During the study period patients become possibly more adherent to VKA which can result in a lower mean dose of VKA needed for adequate anticoagulation. Therefore the difference in mean daily dose per patient is calculated. As a result of inadequate TTR, patients can be under- or over anticoagulated. Therefore both the time under and above the therapeutic range will be calculated.

Safety monitoring

For safety reasons thromboembolic events and serious bleedings are recorded. Recording is performed by staff of the anticoagulation clinic and occurs according to the guidelines of the Federation of Dutch Anticoagulation clinics (FNT).[32] A thromboembolic

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event is defined as: deep vein thrombosis, pulmonary embolism, systemic embolism, stroke, or transient ischemic attack. A serious bleeding is defined as; every intracranial bleeding, every joint bleeding (objectively diagnosed), bleeding resulting in death of patient, blood transfusion, hospital admission, or surgical intervention.[32]

Statistical analyses

The statistician will be blinded for allocation of the participants and report directly to the investigators. Based on the data reported by the statistician the investigators write the final report. TTR calculation will be performed conform the linear method described by Rosendaal et al.[4] If patients are admitted to a hospital or nursing home, the time during hospital or nursing home admission, including the first two weeks after discharge due to the high change of fluctuating INR values, is excluded from the analysis.

Descriptive statistics will be used for patient characteristics. Primary outcomes will be analysed using a mixed-effects model with the intervention, time in therapeutic range before the index date, MDD system at baseline as covariates and pharmacy as random effect. Independent sample *t*-tests will be used for normally distributed continuous variables. Non-normally distributed data will be tested with the Mann-Whitney U test. Pearson chi-squared test will be used for categorical variables. Paired t-tests will be used for intra-individual outcomes. Sensitivity analyses will be performed to assess the influence of missing data. Additionally, sensitivity analyses with different cut-off points for TTR before randomisation, MARS and age will be performed. A two-sided p-value < 0.05 will be considered statistically significant.

Predefined subgroup analyses

Subgroup analysis will be performed for patients with an MDD system in use before randomisation compared to users of manual prescriptions before randomisation (Table 3). Additionally, subgroup analyses will be made based on the scores of the GFI, BMQ, Mini-Cog, MARS and MMC.

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TABLE 3: Overview of the different subgroups receiving medication via an MDD systems or manually dispensed

Group	Dispensing before study	Intervention or control group	Dispensing during study
1	An MDD system, VKA manually	Control	An MDD system, VKA manually
2	All medication was manually dispensed	Control	All medication is manually-dispensed
3	An MDD system, VKA manually	Intervention	All medication is dispensed via an MDD system, including VKA
4	All medication was manually dispensed	Intervention	All medication is dispensed via an MDD system, including VKA

Ethics and Confidentially

The Medical Ethics Review Committee (METC) of the Leiden University Medical Centre (LUMC) has considered the research proposal and concluded the Dutch Medical Research Involving Human Subjects Act (WMO) not applicable. In addition, the study protocol was approved by the Institutional Review Board of UPPER, division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University. To protect patients identity, patients are assigned an unique study number. The signed informed consents will be stored separately from the coded study data by the investigators. The trial is registered at the Dutch National Trial Register (www.trialregister.nl) under the identifier NTR 5883.

Discussion

Dosing aids, including MDD systems, are used to support patients with their medication use. Different studies have shown that dosing aids can improve outcomes like medication adherence, HbA1c levels and blood pressure control.[17] These studies predominantly used pill-boxes and dosettes as dosing aids. It seems reasonable to assume that MDD systems would give comparable results, but evidence has not yet been published. In this study the effect of MDD systems will be described on TTR in patients with a low quality of anticoagulation. The TTR is considered as a strong outcome measure because it is objective, based on a frequently measured parameter (INR), uniform for all patients independent of age and strongly associated with thromboembolism and bleedings.

In 2016, Dumas et al. published an observational cohort study on the effect of dosing aids (no dosing aid, filled by the patient or filled by the pharmacist) in new warfarin users.[33] The primary outcome was the percentage of patient with a TTR > 60%. No differences

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were found between the three groups. The study differs on important aspects from our study. First, in our study patients are eligible when treated with VKAs over 9 months and report a TTR < 65%, thereby focussing on patients with suboptimal TTR. Second, patients in our study are randomised to either the intervention or control group. Third, patients in our study had to use five or more medications. Thereby selecting patients with polypharmacy who have a higher chance on medication mismanagement. Fourth, in our study we use an MDD system which is automatically filled instead of a manually filled pill-box. Manually filled pill-boxes are at a higher risk of dispensing errors and are time consuming to prepare.

Patients are randomised to either the intervention group or control group. For the intervention group patients receive their drugs via an MDD system instead of manually dispensed drugs. Changing the packaging to MDD may also influence adherence to concomitant therapies (e.g., the effectiveness of antihypertensive treatment may improve when patient's adherence is increased, potentially causing hypotension when patients adherence was very low before the start of MDD). To evaluate potential effect on the effectiveness and safety of medication after the start of the MDD system, an evaluation moment by the community pharmacy is considered usual care according to the guideline of the Royal Dutch Pharmacists Association (KNMP) 'Pharmaceutical care for patients with dosing aids'.[15] Additionally, improved adherence to VKAs could also lead to possible changes in INR values. This is obviated by the strict supervision of the Leiden Anticoagulation Clinic. The dosage of VKAs will be adjusted if INR values deviate from therapeutic range after dispensing the VKAs via an MDD. Changes in de dose of VKAs will therefore be a secondary outcome of the study.

This study has also some potential limitations. Ideally, patients enrolled in a prospective randomised controlled trial are blinded for group allocation. Due to the nature of the intervention blinding is impossible. Along with patients, community pharmacists are aware of the patient's group allocation. However, the physicians of the Leiden Anticoagulation Clinic, are not informed of study participation, thereby minimizing possible treatment bias. Also the statistician is unaware of group allocation for an independent data analysis. Second, a wide variety of variables is associated with a reduced TTR.[34] During the patient interviews multiple variables are collected, but there are many factors possibly affecting the TTR. Despite the study design differences on baseline from which we are unaware cannot be ruled out. Third, a potential limitation is the time between the selection of possible eligible patients and the index date. When the period between selection date and index date becomes longer, the chance increases, due to natural improvement, that patients have a TTR > 65% in the period 6 months before the index date. Therefore the Leiden Anticoagulation Clinic will make

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a new selection of potential eligible patients every 3-months. Fourth, patients must give informed consent to participate. Therefore participating patients might not be representative for the whole study population as only motivated patients are willing to participate. As a consequence, the TTR from patients in the control group might also improve because they were alerted about their non-adherence. Last, the VKA schemes for only the intervention patients were prolonged with three days. Small adjustments of the VKA dosing scheme were effectuated three days after the INR assessment. This can result in a theoretical small decrease of the TTR in the intervention group. However, when it is medically necessary to adjust the VKA dosage the same day of the INR assessment, the Leiden Anticoagulation Clinic informs the community pharmacy by telephone in order to adjust the number of VKA tablets in the MDD system.

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Declarations

Ethics approval and consent to participate:

The Medical Ethics Review Committee (METC) of the Leiden University Medical Centre (LUMC) has considered the research proposal and concluded the Dutch Medical Research Involving Human Subjects Act (WMO) not applicable. In addition the study protocol was approved by the Institutional Review Board of UPPER, division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University. Patients gave written informed consent.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interest

SIR Institute for Pharmacy Practice and Policy received an unconditional grant for the PhD project about multidose drug dispensing to conduct this research.

Funding

This study is performed as part of a larger PhD project on multidose drug dispensing. This project received unrestricted funding from The Royal Dutch Pharmacists Association (KNMP) and from a conjunction of six MDD suppliers (SPITS BV, Apotheek Voorzorg BV, Verpakapotheek, Pluripack, 5 Sterrenapotheek, Brocacef Maatmedicatie BV) in the Netherlands. All intellectual and publication rights are reserved for the investigators.

Authors' contributions

BM, HFK, RvM, FvdM and MB were responsible for the study concept and design. BM drafted the initial version of the manuscript. SB contributed to the statistical analysis plan. All authors contributed to the writing of the manuscript and approve the final manuscript for submission.

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APPENDIX 1. Beliefs about Medicine Questionnaire (BMQ)

- I would like to ask you about your personal views about phenprocoumon
- These are statements other people have made about their medication
- Please indicate the extent to which you agree or disagree with them by placing a cross in the appropriate box.
- There are no right or wrong answers. I am interested in your personal views.
- Please only cross one box per question.

	Fully disagree	**Disagree**	**uncertain**	**agree**	**Fully agree**
My health, at present, depends on the use of phenprocoumon	○	○	○	○	○
Having to take phenprocoumon worries me	○	○	○	○	○
My life would be impossible without phenprocoumon	○	○	○	○	○
Without phenprocoumon I would be very ill	○	○	○	○	○
I sometimes worry about the long-term effects of phenprocoumon	○	○	○	○	○
Phenprocoumon is mystery to me	○	○	○	○	○
My health in the future will depend on phenprocoumon	○	○	○	○	○
Phenprocoumon disrupts my life	○	○	○	○	○
I sometimes worry about becoming too dependent of phenprocoumon	○	○	○	○	○
Phenprocoumon protect me from becoming worse	○	○	○	○	○

APPENDIX 2. Medication Adherence Report Scale (MARS)

	never	**rarely**	**sometimes**	**often**	**always**
Do you ever forget to take phenprocoumon?	○	○	○	○	○
Do you alter the dose of phenprocoumon by yourself?	○	○	○	○	○
Do you sometimes stop taking phenprocoumon?	○	○	○	○	○
Do you ever decide to miss out a dose of phenprocoumon?	○	○	○	○	○
Do you take less phenprocoumon than prescribed?	○	○	○	○	○

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APPENDIX 3: Groningen Frailty Indicator

	For questions 1-4: Is the patient able to carry out these tasks without any help? (The use of help resources such as walking stick, walking frame, wheelchair, is considered independent)	Yes	no	
1	Shopping		✓	
2	Walking around outside (around the house or to the neighbours)		✓	
3	Dressing and undressing		✓	
4	Going to the toilet		✓	
5	What mark does the patient give himself/herself for physical fitness? (scale 0 to 10) 0 – 6 = 1 point 7 – 10 = 0 points			
		Yes	no	
6	Does the patient experience problems in daily life due to poor vision?	✓		
7	Does the patient experience problems in daily life due to being hard of hearing?	✓		
8	During the last 6 months has the patient lost a lot of weight unwillingly?	✓		
	(3 kg in 1 month or 6 kg in 2 months)	✓		
9	Does the patient take 4 or more different types of medicine?	✓		
		Yes	Sometimes	No
10	Does the patient have any complaints about his/her memory?	✓	✓	
11	Does the patient sometimes experience an emptiness around him/her?	✓	✓	
12	Does the patient sometimes miss people around him/her?	✓	✓	
13	Does the patient sometimes feel abandoned?	✓	✓	
14	Has the patient recently felt downhearted or sad?	✓	✓	
15	Has the patient recently felt nervous or anxious?	✓	✓	

✓ indicates one point
If scored ≥ 4 points, the patient is assessed as frail

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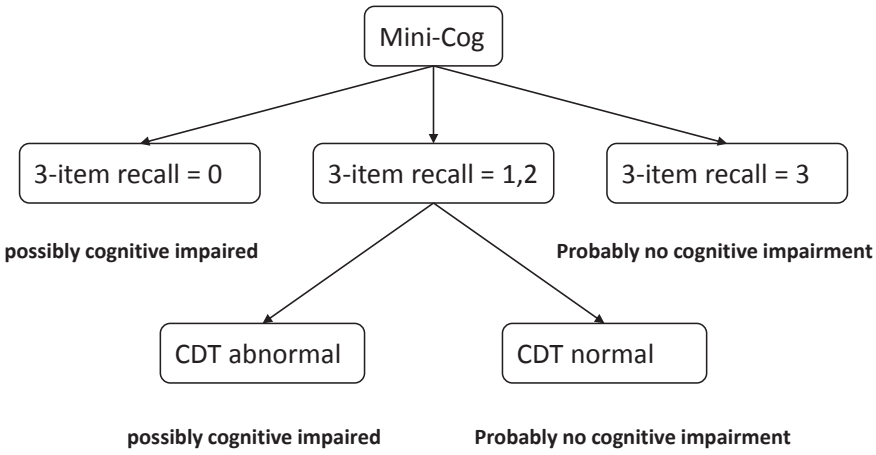
APPENDIX 4: Mini-Cog

Algorithm of the Mini-Cog. Items to be recalled: apple, coin and table. CDT: clock drawing test.



APPENDIX 5: Medication Management Capacity questionnaire

	Question	Yes	No
1.	Patient estimates that he has lost the ability to manage his medication	✓	
2.	Patient indicates to forget medication on a regular basis	✓	
3.	Patient encounters a problem with the packaging of the medication	✓	
4.	Patient finds it difficult to manage his drug regimen	✓	
5.	Patient finds it difficult to order the medication in time	✓	
6.	Patient cannot recall the correct indication of > 75% of their medication	✓	
7.	Patient does not designates all medication correctly	✓	
8.	Patient lives alone at home	✓	
9.	Patient receives home care but is self-responsible for his medication regimen	✓	

Medication Management Capacity questionnaire. ✓ indicates a potential problem

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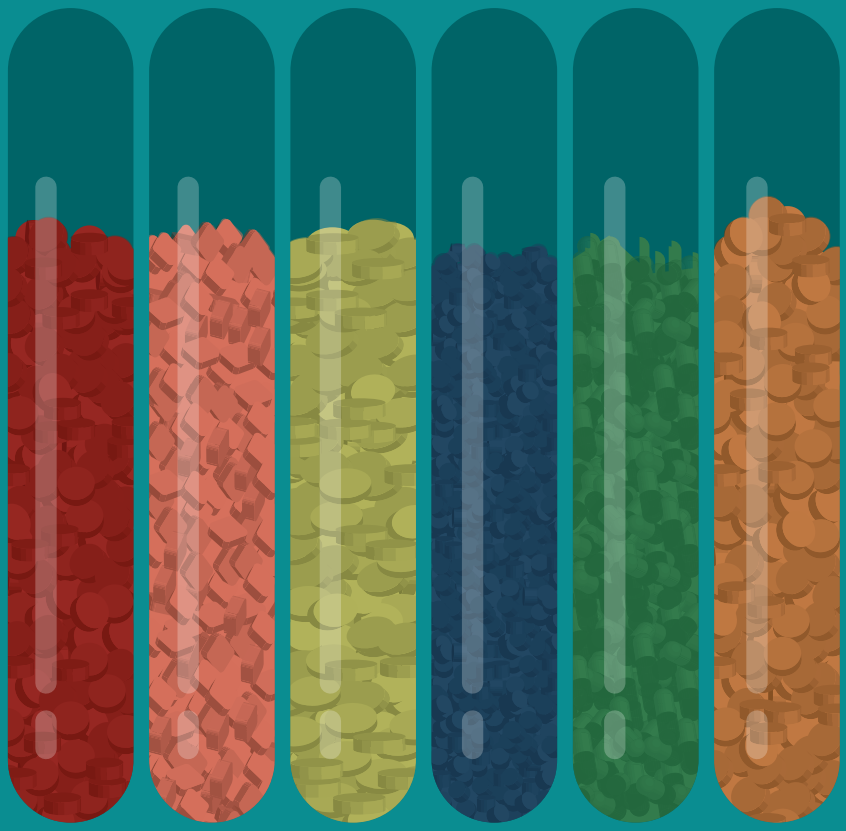

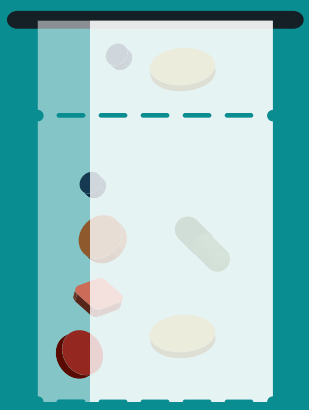

Chapter 7

Effect of multidose drug dispensing on the time in therapeutic range in patients using vitamin K antagonists: a randomised controlled trial

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Abstract

Background: A high number of vitamin K antagonists users have a low proportion of time in therapeutic range resulting in a high number of bleedings and thromboembolism.

Objective: Can the quality of anticoagulation be improved by dispensing vitamin K antagonists via multidose drug dispensing (MDD)?

Method: A randomised controlled trial in the Netherlands. Patients who used vitamin K antagonists (>9 months), ≥ 65 years of age and with a time in therapeutic range < 65% were eligible for inclusion. All oral drugs, including vitamin K antagonists, were dispensed via MDD. In MDD systems, all oral chronic medication intended for one dosing moment is automatically packed in plastic disposable pouches. Controls received vitamin K antagonist by manual-dispensing. The difference in time in therapeutic range between the six months after- and six months before the index date. A mixed-effects model with the intervention, time in therapeutic range before the index date, MDD system at baseline as covariates and pharmacy as random effect.

Results: 179 patients were included. Mean age was 80.0 (SD 6.9) years. Mean time in therapeutic range during the study was 79.2±18.0% in the intervention group and 72.5±20.1% in the control group. The intervention resulted in a 5.6% [95%CI: 0.1 – 11.1; P=0.048] increase in time in therapeutic range compared to the control group. Per protocol analysis resulted in a 8.3% [95%CI: 0.99 – 15.61; P=0.026] increase in time in therapeutic range compared to the control group. No differences were seen between the groups in the number of bleedings or thromboembolic events.

Conclusion: The quality of anticoagulation can be improved with the use of MDD systems.

Trial registration: The trial is registered at the Dutch trial register (NTR5883). Registered at 30 May 2016. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5883

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Introduction

Despite the introduction of the non-vitamin K antagonist oral anticoagulants (NOACs), vitamin K antagonists (VKAs) are still used extensively.[1] VKAs are highly effective drugs to treat and prevent thromboembolism.[2,3] The management of VKA therapy differs between countries but always consists of assessment of the International Normalized Ratio (INR) followed by adjustment of dosing regimens. From consecutive INR values, the time in therapeutic range (TTR) can be calculated using the Rosendaal method.[4] The TTR is a measure for the quality of VKA therapy. A low TTR is correlated with an increased risk of bleeding and thromboembolism.[5-7] In the Netherlands, monitoring is performed by specialized anticoagulation clinics. Despite intensive support from these specialized anticoagulation clinics, around 20% of the patients have a TTR < 65% which is considered inadequate.[5,8]

A low TTR can be caused by a variety of reasons that influence pharmacokinetics of VKAs like comorbidities, co-medication, alcohol, genetics, food etc.[9,10] Another explanation is a reduced medication adherence to VKAs, possibly caused by the complexity of the VKA dosing regimens.[11] Especially older persons frequently experience problems managing their medication. These problems can be due to a wide variety or combinations of reasons (e.g., complex dosing regimens, polypharmacy, cognitive dysfunction or impaired manual dexterity).[12-14]

Patients with a reduced MMC may benefit from dosing aids.[15-17] In the Netherlands, the majority of patients in need of dosing aids receive their drugs via automated multidose drug dispensing (MDD).[16] In MDD systems all oral solid drugs are automatically packed in disposable plastic sachets. These disposable sachets are labelled with patient data, content, date, and time of intake.[18] Not every drug is suitable to be dispensed via an MDD system due to practical packaging issues (e.g., sachets, liquids, eye drops, suppositories) or fluctuating dosing regimens, like VKA. These drugs generally remain manually dispensed in their original packaging alongside the MDD system. It seems counter-intuitive to dispense VKAs, which are one of the most complex drugs to manage, outside an MDD system. However, by dispensing the VKA via an MDD system, the medication adherence and consecutively the TTR might be improved.[19] For a number of patients, VKAs are already dispensed via an MDD system. However, it has never been shown that this method improves the TTR. Therefore the aim of the study was to determine the effect on the quality of anticoagulation of dispensing VKAs via an MDD system on the TTR.

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Methods

Design and setting

This was a randomized controlled trial with two study groups (allocation ratio 1:1) in 18 community pharmacies located in the catchment area of the Leiden Anticoagulation Clinic. The study was designed conform the SPIRIT statement.[20]

Intervention

Patients in the intervention group received all chronic solid oral drugs via an MDD system, including VKAs. Patients in the control group received VKAs via manual dispensing. Control patients were allowed to use an MDD system at baseline, but the VKA had to be manually dispensed. To enable community pharmacies to distribute VKAs via an MDD system, dosing schemes were sent both to the patient and the community pharmacy. If a patient receives the VKA via manual dispensing, the new VKA dosing schemes starts the day after the INR assessment. This short period of time hampers dispensing VKAs via an MDD system because a pharmacist needs three days to order or produce the MDD system. Therefore, the shortest VKA dosing schemes for intervention patients were automatically extended by the Leiden Anticoagulation Clinic with three days (from seven to 10 days). These three extra days enabled the community pharmacist to order or produce the MDD system which included the VKA. If a dose adjustment of the VKA dosing regimen in intervention patients was needed, adjustment was deferred until the start of the new dosing scheme (four days after the INR assessment). If a physician of the Leiden Anticoagulation Clinic considered deferred adjustment with three days inappropriate, the community pharmacy was informed by telephone and the MDD system was manually adjusted by the community pharmacy the same day.[21]

Participants

Every three months the Leiden Anticoagulation Clinic selected patients ≥ 65 years of age with a chronic indication for VKAs and a low TTR (< 65%) over the preceding six months.[7] Because of frequently fluctuating INR values during the first three months of VKA use, patients with VKA use shorter than nine months (3 + 6 months) were excluded. In addition, patients who performed INR measurements and dosing independently were excluded. After the first screening, community pharmacists received a list of potential eligible patients. These patients were screened on additional inclusion and exclusion criteria by the community pharmacist. To increase the likelihood that a low TTR was caused by unintentional non-adherence, patients had to be use a minimum of five chronic drugs. Patients with home-care responsible for the administration of the patient's medication, or who already received their VKA via an MDD system or

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who received chemotherapy were excluded. Because the Leiden Anticoagulation Clinic performed the screening on a low TTR but community pharmacists performed the actual inclusion, a patient's TTR could already be higher than 65% over the past six months on the patient's index date.

Patient inclusion

Eligible patients received an information letter by postal mail from the community pharmacist. Within one week after the information letter patients were invited by telephone to participate. If interested, patients were visited at home for written informed consent and study inclusion. At the start of the study, the patient's cognition and frailty were assessed with the Mini-Cog and the Groningen Frailty Indicator (GFI), respectively. [22,23]

Randomisation and blinding

Randomisation (1:1) was stratified on MDD use at baseline, but the VKA had to be manually dispensed. Therefore, two randomisation sequences containing 208 numbers, one for MDD use at baseline and one for manually dispensed drug use at baseline, were generated using SPSS (version 23.0, SPSS Inc., Chicago, IL, USA). After the community pharmacist obtained written informed consent, researchers (BM) were contacted for group allocation. Group allocation was not blinded for patients, pharmacists and investigators. Because the procedures of MDD patients differ from the normal procedures, the physicians of the Leiden Anticoagulation Clinic were aware that a patient received the VKA via an MDD system but unaware of the patient's study participation. Study outcomes were analysed by an independent statistician (SVB) who was blinded for group allocation.

Sample size calculation

To demonstrate an absolute difference in TTR of 10% for the primary outcome with an alpha of 0.05, a standard deviation of 23 and a power of 80%, a total number of 83 patients in both the intervention and the control group were needed. To compensate for loss to follow-up we aimed at an additional 25% extra patients in both study groups which resulted in a total aim of 208 patients.

Primary outcomes

The primary outcome was the difference in TTR improvement between the intervention and control group. TTR was calculated over a period of six months, both before the index date and after the index date. The index date for the intervention was the first day a VKA was dispensed via an MDD system. The index date for control patients was the date that the patient signed informed consent.

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Secondary outcomes:

A secondary outcome was the number of patients with an adequate quality of anticoagulation (TTR ≥ 65%) over the six months after the index date. Patients with an inadequate TTR can be under- or over anticoagulated. Therefore, both the time under (TuTR) and time above the therapeutic range (TaTR) were calculated. Other secondary outcomes were the number of high INR assessments (> 4.0), the number of vitamin K doses for an uncontrolled INR and the mean number of INR control visits.

Safety monitoring

For safety reasons, thromboembolic events, all bleedings (minor and major) and hospital admissions were recorded. Recording was performed by staff of the anticoagulation clinic and occurred according to the guidelines of the Federation of Dutch Anticoagulation clinics.[24]

Statistical analyses

Data were analysed using statistical software packages SPSS (version 23.0, SPSS Inc., Chicago, IL, USA) and R (version 3.4.4). Based on the data reported by the statistician, the investigators wrote the final report. Information on treatment indications, target INR ranges, INR measurements, bleedings, thrombosis and hospital admissions were obtained from the Leiden Anticoagulation Clinic. TTR calculation was performed conform the linear method described by Rosendaal.[4] The time during hospitalization, including the first two weeks after discharge were excluded from the analyses.

Primary outcomes were analysed using a linear mixed-effects model (intervention, MDD use at baseline, the TTR before the index date as covariates and the participating pharmacies as random effect). MDD use at baseline was included in the model as randomisation was stratified on MDD use. TTR before the index date was included in the model to compensate for any baseline differences. A TTR cannot be higher than 100%, thereby, the higher a patient's TTR is at baseline, the less likely an improvement becomes. Last, community pharmacies were included as random effects to compensate for potential differences in used procedures between the community pharmacies. Intention to treat (ITT) analyses were performed with all patients who had at least 2 INR assessments after the index date. A per protocol (PP) analysis was performed with patients with a TTR < 65% in the six months before the index date and who completed the study period as intended.

Categorical values were calculated using a mixed-effects logistics regression model (intervention, MDD use at baseline, the TTR before the index date as covariates and the participating pharmacies as random effect). Non-normally distributed secondary

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continuous outcomes were analysed with a linear quantile mixed-effects model (intervention, MDD use at baseline, TaTR or TuTR before index date as covariates and participating pharmacies as random effect.) Countable secondary outcomes were analysed using mixed-effects Poisson regression model (intervention, MDD use at baseline as covariates, participating pharmacies and study number as random effect, and number of control visits as off-set parameter). Safety outcomes were analysed using a quasi-Poisson regression model (intervention and MDD use at baseline as covariates).

Predefined subgroup analyses

Subgroup analyses were performed for patients using an MDD system or manually dispensed medication at baseline.

Ethics approval

The Medical Ethics Review Committee (METC) of the Leiden University Medical Centre (LUMC) concluded the Dutch Medical Research Involving Human Subjects Act (WMO) not applicable. The trial is registered at the Dutch National Trial Register (www.trialregister.nl) under the identifier NTR 5883. In addition, the study protocol was approved by the Institutional Review Board of UPPER, division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University. To protect the patient's privacy, only age, gender and study number were documented.

Results

Of 528 invited patients, 179 (34%) gave informed consent (Figure 1). Forty eight percent was female and mean age was 80.0 years (SD = 5.9). Study enrolment lasted from June 2016 to September 2017. The last patient completed the study in January 2018. The number of included patients per pharmacy ranged from 1-28 (mean 9, SD = 5). The mean number of days between the selection by the Leiden Anticoagulation Clinic and the start of the intervention was 67 days for the intervention group and 57 days for the control group (p = 0.054). As a consequence of this delay, 57 (32%) patients had a TTR in the 6 months before the index date which was higher than the predefined 65%. The study groups were similar at baseline with the exception of the target INR range (Table 1).

As all patients had at least two INR assessments after the index date, all patients were included in the ITT analysis. Fourteen patients (7.8%) did not complete the six months study period as intended (five patients died, five patients switched to a NOAC and four patients returned to manual dispensing). No dropout differences were observed (p=0.53). The study flow is depicted in Figure 1.

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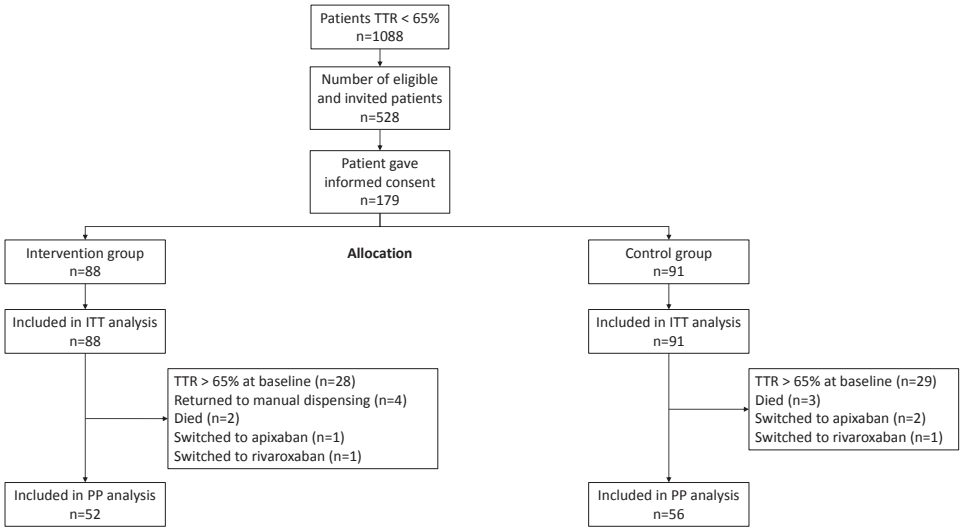

FIGURE 1: Study flow

Abbreviations: n = number; ITT = intention to treat; TTR = time in therapeutic range; PP = per protocol

Primary outcomes

The TTR improved for both the intervention and the control group during the six months study period (Table 2). In the intervention group an additional increase in TTR of 5.6% [95%CI: 0.1 - 11.1] was observed compared with the control group. For the PP analysis, 71 patients were excluded (see Figure 1). The mean TTR at baseline in the intervention group (n=52) was 50.7% (SD ± 10.6%) and the mean TTR in the control group (n=56) was 47.6% (SD ± 12.4%) (p=0.16). In the PP analysis, an additional increase in TTR of 8.3% [95%CI: 1.0 - 15.6] was observed.

Secondary and safety outcomes

Eighty-one percent (n=71) of the patients in the intervention group had a TTR > 65% during the study period compared with 65% (n=59) of the patients in the control group (adjusted OR = 2.05 [95%CI: 1.01 - 4.25]). The distribution of patients per 10%-TTR range is graphically presented in Figure 2. The largest increase in number of patients was observed in the group of patients with a TTR between 90% - 100% during the six months study period (adjusted OR = 2.19 [95%CI: 1.12 - 4.28]). An overview of the other secondary and safety outcomes is given in Table 3. No difference was seen in the average dose of VKA between the intervention and control group (p=0.13). The intervention resulted in a lower median TuTR in the intervention group compared with the control group.

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TABLE 1: Baseline characteristics over the six months before the index date

	Intervention (n=88)	**Control (n=91)**
Age mean (± SD)	79.8 (7.1)	80.2 (6.7)
Female n (%)	42 (48)	43 (47)
MDD system in use n (%)	35 (40)	32 (35)
Frail n (%)	46 (54)	43 (53)
Cognition impaired n (%)	29 (34)	22 (25)
Treatment indication atrial fibrillation n (%)	80 (91)	75 (82)
Target INR range 2.0 – 3.0 n (%)	85 (97)	78 (86)
Target INR range 2.5 – 3.5 n (%)	3 (3)	13 (14)
TTR mean (± SD)	60.8 (16.4)	55.9 (18.0)
TuTR median (IQR)	13.8 (0; 29.8)	11.6 (0; 30.9)
TaTR median (IQR)	21.0 (4.1; 30.4)	22.7 (11.1; 38.1)
Number of INR control visits mean (± SD)	9.42 (3.7)	10.0 (4.0)
Number of INR assessments > 4.0 (n)	40	63
Number of bleedings (n)	26	14
Number of thromboembolic events (n)	2	2
Number of hospital admissions (n)	11	15
	Intervention (n=83)	**Control (n=83)**
Number of drugs mean (± SD)	10.4 (4.1)	10.6 (4.2)
Number of vitamin K doses (n)	8	10
Most used drugs		
Beta blocking agents n (%)	63 (76)	69 (83)
Proton pump inhibitor n (%)	55 (66)	56 (67)
HMG CoA reductase inhibitors n (%)	59 (71)	52 (63)
High-ceiling diuretics n (%)	33 (40)	35 (42)
ACE inhibitors n (%)	25 (30)	30 (36)
Drugs for constipation n (%)	25 (30)	29 (35)
Vitamin D n (%)	23 (28)	29 (35)
Dihydropyridine calcium channel blockers n (%)	24 (29)	22 (27)
Angiotensin II antagonists n (%)	17 (20)	27 (33)
Oral blood glucose lowering drugs n (%)	24 (29)	18 (22)

Abbreviations: SD = standard deviation; MDD = multidose drug dispensing; TTR = Time in Therapeutic Range; TuTR = Time under Therapeutic Range; TaTR = Time above Therapeutic Range; INR = International Normalized Ratio; ATC = Anatomical Therapeutic Chemical; IQR = Interquartile Range

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A subgroup analysis in patients with an MDD system at baseline resulted in an additional increase in TTR of 6.2% [95% CI = -3.13 – 15.48]. Among patients who used manually dispensed drugs at baseline, an additional increase in TTR of 5.1% [-2.01 – 12.24] was observed (p-value for interaction = 0.86).

TABLE 2: Main outcomes for intervention and control patients in TTR during the six months after the index date.

Analysis		Intervention	Control	Effect of intervention mean (95%CI)	p-value
Intention To Treat Intervention (n=88) Control (n=91)	TTR after index date mean (± SD)	79.2 (± 18.0)	72.5 (± 20.1)	+ 5.6% (0.1; 11.1)	**0.048**
Per Protocol Intervention (n=52) Control (n=56)	TTR after index date mean (± SD)	79.4 (± 18.6)	69.9 (± 20.3)	+ 8.3% (1.0; 15.6)	**0.026**

Effect of intervention with 95%CI (adjusted for TTR before index date, MDD at inclusion and pharmacy)
Abbreviations: n = number; TTR = Time in Therapeutic Range; SD = standard deviation; CI = confidence interval

FIGURE 2: Distribution of intervention and control patients in the six months before the index date and the six months after the index date

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TABLE 3: Secondary and safety outcomes for intervention and control patients during the six months study period.

		Intervention (n=88)	Control (n=91)	Effect of intervention (95%CI)	p-value
TuTR median (IQR)	Value	0.6 (0; 13.3)	7.2 (0; 23.9)	- 5.9 (-11.0; -0.86)	**0.02** [a]
	Estimated value (95%CI)	7.2 (3.2; 11.1)	13.5 (8.7; 18.3)		
TaTR median (IQR)	Value	5.3 (0; 17.8)	6.7 (0; 21.4)	- 0.8 (-4.2; 2.6)	0.65 [a]
	Estimated value (95%CI)	10.0 (6.3; 13.7)	11.4 (6.9; 15.9)		
Number of control visits mean (± SD)	Value	7.8 (3.3)	8.3 (3.7)	- 0.3 (-1.3; 0.6)	0.50 [b]
	Estimated value (95%CI)	8.1 (7.4; 8.5)	8.3 (7.6; 9.1)		
INR assessments > 4 % (n/total INR assessments)	Value	2.2 (15/685)	4.4 (33/756)	0.7 (0.3; 1.34)	0.29 [c]
	Estimated value (95%CI)	1.3 (0.6; 2.4)	3.2 (2.0; 4.9)		
Vitamin K doses * % (n/total INR assessments)	Value	1.7 (11/651)	1.4 (10/708)	1.4 (0.4; 5.2)	0.61 [c]
	Estimated value (95%CI)	0.77 (0.18; 2.14)	0.38 (0.01; 1.45)		
Bleedings (n)	Value	17	10	1.7 (0.6; 5.6)	0.33 [d]
	Estimated value (95%CI)	16.6 (7.8; 30.0)	9.6 (2.4; 23.6)		
Thromboembolic events (n)	Value	1	0	n.a.	n.a.
	Estimated value (95%CI)	n.a.	n.a.		
Hospital admissions (n)	Value	14	12	1.2 (0.5; 3.0)	0.67 [d]
	Estimated value (95%CI)	13.7 (5.8; 26.3)	11.8 (6.1; 19.8)		

[a] linear quantile mixed-effects model
[b] linear mixed-effects model
[c] mixed-effects Poisson regression model. Number of control visits in six months before index date as off-set parameter
[d] quasi-Poisson regression model
n.a. due to small number of observations
* data available for 83 intervention and 83 control patients
Abbreviations: CI = confidence interval; TuTR = time under therapeutic range; TaTR = time above therapeutic range; SD = standard deviation; INR = International Normalised Ratio; n = number; n.a. = not applicable

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Discussion

This study shows that dispensing VKAs via an MDD system can improve the patient's quality of anticoagulation compared to manual dispensing of VKAs. The intervention resulted not only in a an increase in TTR but also in a higher number of patients with a TTR between 90 - 100%. The higher TTR was reflected by a lower time under the therapeutic range in the intervention group compared to the control group, which may result in a lower number of thromboembolic events. This was not observed on the safety outcomes as the study was not powered on safety outcomes. The intervention was well accepted as only four patients (5%) returned to manual dispensing of the VKA.

The intervention resulted in a TTR increase of 5.6%. Among patients who still fulfilled the inclusion criterion of a TTR < 65% at index date, the increase was even higher. As dispensing VKAs via an MDD system is costly and time consuming, it should only be applied when a clinical relevant effect can be expected (e.g., low TTR). The correlation between the TTR and clinical outcomes like bleedings and thromboses is strong. Also in our study, a reduction in the number of bleedings was observed, both in the intervention and control group. However, this was not statically different between the intervention and control group. About the interpretation of the effect can be debated as no minimal clinical effect on TTR is defined. The effect of the TTR on the number of bleedings has been shown to be linear; the higher the TTR, the lower the number complications.[7,25] An increase in TTR of 5% will reduce the number of thromboembolic events, major bleeding events and deaths in a large population.[25,26] Ideally, a cost-effectiveness analysis would be performed including the additional costs of the MDD systems and potential health savings. The start of an MDD system seems especially interesting for patients with a low TTR not provoked by an explanatory cause (e.g., long lasting flue, hospital admission for surgery). In addition, unintentional non-adherence must be suspected as MDD systems are unlikely to improve intentional non-adherence.[16,18,27]

A previous retrospective database study by Van Rein et al. reported that dispensing VKAs via an MDD system could temporally improve the patient's TTR compared to users of manually dispensed VKAs.[19] The effect in this retrospective study was present after one month but not after four or six months. The effect of an MDD system on the patient's TTR was lower in the study by Van Rein et al. compared to our study. A major limitation in the study by Van Rein et al. was that MDD systems were not specifically initiated to improve the TTR. Finding identical control patients is almost impossible as MDD systems are initiated for patients with a reduced medication management capacity.[15] To eliminate potential confounders, a randomised control trial is more appropriate. A second study by Dumas et al. evaluated the effect of a different dosing aid, a pill-box, on the quality

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of anticoagulation in naïve VKA users.[28] No differences were seen between the three study arms in this prospective observational cohort study. The study differed on some important aspects from our study. First, our study focused on patients with a low quality of anticoagulation despite long term use of VKAs and not on naïve VKA users. Second, as a result of the non-randomised study design of Dumas et al., large differences in age, gender and education were observed between the study groups which hamper conclusions.

Not only in the intervention group an improvement of the TTR was observed, also the TTR in the control group improved. This might be explained by two known phenomena. First, all patients received written information about their low quality of anticoagulation and were visited at home for written informed consent and inclusion. Thus awareness on the importance of therapy adherence may also have risen in the control group. Second, regression to the mean may have been stronger in the control group as the mean TTR before the index date was lower compared to the intervention group. Ideally, a third group who did not receive any information about the study or their low quality of anticoagulation was incorporated in the study. However, without informed consent, no patient data can be used under the Dutch Medical Research Involving Human Subjects Act.

Our study had some particular strengths. First, the only introduced difference between the intervention and control group was the dispensing of the VKA via an MDD system. By using an existing network of care with regular patient follow-up, the effect of dispensing VKAs via an MDD system was specifically determined. All patients continued to receive standard care from the anticoagulation clinic. Second, the TTR is an objective outcome measure strongly correlated with clinical outcomes.[7, 25, 26] Last, included patients were representative for the type of patients that are eligible for MDD as comparable patient characteristics were found in an observational study among new MDD users.[15]

Besides the strengths, our study had also some potential limitations. First, the protocols used to adjust VKA regimens during the study differed between users of MDD systems and manually dispensed medication. VKA dose regimens were automatically prolonged with three days for patients allocated to the intervention. Theoretically, this can lead to a slightly lower TTR for MDD patients which could have reduced the positive effect of the intervention. Second, we did not include the intended number of patients. During the trial, lower loss to follow-up percentages were observed than anticipated. Therefore, inclusion was ceased at the moment that the required number of patients with sufficient follow-up were included. Last, despite randomization, more patients in the control group had a target INR range of 2.5 – 3.5. A higher target INR range is associated with

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a lower TTR which might explain the lower TTR preceding the index date in the control group.[8] As mentioned before, this may also imply that control patients were more likely to regress to the mean.

Conclusion

The quality of anticoagulation can be improved by dispensing VKAs via an MDD system, especially in patients with a TTR < 65%. The improved quality of anticoagulation was reflected by an improved TTR and a lower TuTR. No differences were found between the intervention and control group on the number of bleedings or thromboembolic events.

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Competing interest

B. Mertens received an unconditional grant for the PhD project about multidose drug dispensing to conduct this research.

Funding

This study was performed as part of a larger PhD project on multidose drug dispensing. The project received unrestricted funding from The Royal Dutch Pharmacists Association and from a conjunction of MDD suppliers (SPITS BV, Apotheek Voorzorg BV, Verpakapotheek, Pluripack, 5 Sterrenapotheek, Brocacef Maatmedicatie BV) in the Netherlands. All intellectual and publication rights are reserved for the investigators.

Role of the Funder/Sponsor

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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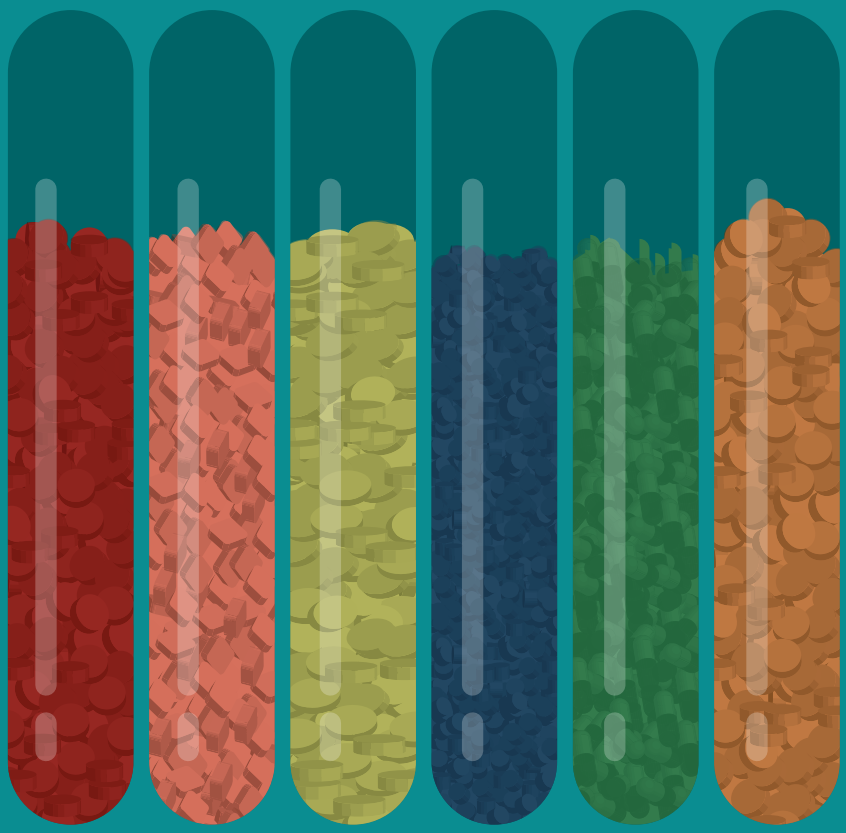

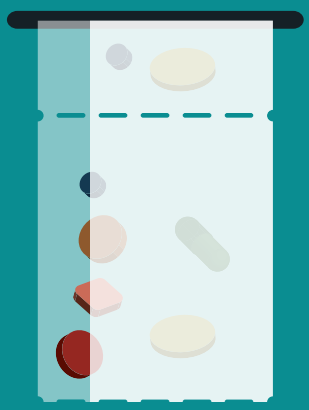

Chapter 8

Which patients benefit most from dispensing vitamin K antagonists via multidose drug dispensing: a subgroup analysis of a RCT

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Abstract

Aim: It was shown that patients' time in therapeutic range (TTR) can be improved by dispensing vitamin K antagonists (VKAs) via multidose drug dispensing (MDD). The aim of the present study was to explore which subgroups of patients benefitted most from dispensing VKAs via an MDD system.

Methods: Patients in the intervention group received all drugs, including VKAs, via an MDD system. Controls received their VKAs via manual dispensing. Subgroup analyses used a mixed-effects model with the intervention, MDD use and the TTR at baseline as covariates and participating pharmacies as random effect.

Results: 165 patients were included. The intervention was more effective (p-value for interaction = 0.03) in patients with two or more potential medication management problems (11.6% TTR increase [95%-CI: 4.31–18.88]) compared to patients with less than two medication management problems (-2.6% TTR increase [95%-CI: -11.79–6.63]). The effect of the intervention tended to result in a higher TTR increase in frail patients (8.2% [95%-CI: 0.35–15.99]) compared to non-frail patients (0.5% [95%-CI: -8.12–9.13]), in patients aged ≥ 80 years (8.1% [95%-CI: 0.13–16.05]) compared to patients aged 65 – 79 years (3.8% [95%-CI: -4.62–12.19]) and in patients with a low self-reported adherence (10.6% [95%-CI: -0.56–21.68]) compared to patients with an adequate self-reported adherence (3.1% [95%-CI: -3.95–10.17]). The patient's gender, cognitive function, the number of drugs and patients' beliefs about VKA treatment did not appreciably affect the effect of the intervention.

Conclusion: The initiation of an MDD system was more effective in patients with a reduced medication management capacity. Also patients ≥ 80 years of age, frail patients and patients with a low self-reported adherence tended to benefit more.

Trial registration The trial is registered at the Dutch trial register (NTR5883). Registered at 30 May 2016.

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Background

VKAs are highly effective to treat and prevent thromboembolism. Despite the introduction of non-vitamin K antagonists, VKAs are still frequently used.[1-3] The quality of the anticoagulation by VKAs is reflected by the patient's time in therapeutic range (TTR) which can be calculated from consecutive INR values using the Rosendaal method.[4] A low TTR is associated with an increased risk of bleeding and thromboembolism.[5-7] Recently, a randomised controlled trial (RCT) was performed among users of vitamin K antagonists (VKAs) with polypharmacy. The effect of dispensing VKAs via an automated multidose drug dispensing (MDD) system on the patient's TTR was assessed. Overall, the initiation of the MDD system proved to positively affect the TTR.

MDD systems are a special type of dosing aid in which all oral solid drugs are automatically packed in disposable plastic sachets. These disposable sachets are labelled with patient data, content, date, and time of intake.[8,9] MDD systems are frequently used, especially among the oldest patients.[10] MDD systems facilitate the implementation of complex medication regimen with the ultimate goal to improve the medication adherence and medication safety.[9,11] The initiation of an MDD system will only appreciably contribute to the patient's medication adherence if a patient indeed experiences a problem with his medication management.

In the RCT, inclusion criteria were comprehensive and not limited to patients with medication management problems. Therefore, not all patients may have benefited equally from dispensing VKAs via an MDD system. To enable explorative subgroup analyses, baseline characteristics were collected that theoretically could influence the effect of the intervention. The aim of the present study was to identify which subgroups especially benefit from dispensing VKAs via an MDD system.

Methods

Design and setting

A randomized controlled trial with two study groups (allocation ratio 1:1) in 18 community pharmacies located in the catchment area of the Leiden Anticoagulation Clinic. Patients in the intervention group received all chronic solid oral prescription drugs via an MDD system, including VKAs. Patients in the control group received VKAs via manual dispensing in the original packaging. Patients were allowed to use an MDD system use at baseline, but the VKA had to be manually dispensed.

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Participants

Patients monitored at the Leiden Anticoagulation Clinic were quarterly screened on a low TTR (< 65%) over the previous six months.[7] After screening on inclusion (≥ 65 years of age, chronic indication for VKA, VKA use for a minimum of 9 months) and exclusion criteria (self-monitoring of VKA), a list of potential eligible patients was sent to the patient's community pharmacy. Community pharmacists screened the potential eligible patients on the additional inclusion (use of ≥ 5 chronic oral drugs) and exclusion criteria (home-care responsible for the administration of medication). Eligible patients received an information letter by postal mail from the community pharmacist. If interested, patients were visited at home for formal written informed consent and inclusion. During the home visit, the patient's cognitive function (Mini-Cog) and the medication management capacity (MMC) were assessed.[12] Additionally, patients were asked to complete the Beliefs about Medicines Questionnaire (BMQ), Medication Adherence Report Scale (MARS) and Groningen Frailty Indicator (GFI). [13-15]

Cognition

A decreased TTR has been associated with a decreased cognition.[16,17] Therefore, cognition was assessed using the Mini-Cog. The Mini-cog is a combination of a 3-item recall test and a clock drawing test. The Mini-cog is easier to apply compared to the Mini Mental State Examination (MMSE) but well correlated to the MMSE score.[18] Each correct word was awarded 1 point and a correct clock was awarded 2 points. Total scores were dichotomised. Scores of ≤ 2 suggests a cognitive impairment.

Medication management capacity

For a previous study, an extensive questionnaire was designed to identify potential problems in the patient's medication management.[19] For the present study, the questionnaire was shortened to nine questions which were most predictive for a reduced medication management capacity (MMC). Each question was scored a 0 (problem unlikely) or a 1 (possible problem), resulting in a possible score ranging from 0 to 9. Scores were dichotomised based on the median for all patients. For the present study, patients with 0 or 1 potential problem were considered to have an adequate MMC. Patients with 2 or more potential problems were considered to have a reduced MMC.

Beliefs about medicines questionnaire

The BMQ specific consists of 10 questions on a five-point Likert scale (1=fully disagree, 2=disagree, 3=uncertain, 4=agree, 5=fully agree) that cover two domains.[13] Five questions covered the patients' beliefs about the necessity of VKA treatment, the

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other five questions covered the patients' concerns about VKA treatment. To obtain the necessity-concerns differential, the score for the patient's concerns (minimal 5 and maximum 25) was subtracted from the score on the patient's needs (minimal 5 and maximum 25). Based on the median of the necessity-concerns differential, patients were categorised into two groups: patients with a necessity-concerns differential ≥ 5 and with a necessity-concerns differential < than 5.

Patient self-reported adherence

The self-reported adherence was measured with the Medication Adherence Report Scale (MARS). [14] The MARS contains 5 statements on both intentional and unintentional non-adherence which are scored on a five-point Likert scale (1=always, 2=often, 3=sometimes, 4=rarely and 5=never). Scores were dichotomised based on the median score. Patients who scored ≤ 24 were considered as non-adherent and patients who scored 25 points were considered adherent.

Frailty

Frailty has been associated with a reduced TTR and a low medication adherence.[20,21] Therefore, frailty was assessed with the Groningen Frailty Indicator (GFI). The GFI is a validated tool and consists of 15 questions. Each question can be scored with 0 or 1 point. Total scores were dichotomised with a cut-off point of four or more classifying the patient as frail.[15]

Outcomes

The primary outcome was the difference in TTR over the six months after- and six months before the index date. The index date for the intervention was the first day that a patient received the VKA via an MDD system. The index date for control patients was the date that the patient signed informed consent.

Statistical analyses

Analyses were performed using SPSS (version 24.0, SPSS Inc., Chicago, IL, USA). TTR calculation was performed conform the linear method described by Rosendaal.[4] The time during hospital or nursing home admission, including the first two weeks after discharge were excluded from the analyses due to the a high likelihood of fluctuating INR values. All patients who completed the six months study period were included in the subgroup analysis.

Predefined subgroup analyses were performed based on the patient's cognitive function, MMC, MARS and BMQ and frailty. Post-hoc analyses were performed based on gender,

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age and number of drugs in use. The effect of the intervention on the TTR was calculated using a linear mixed-effects model with MDD use at baseline and the TTR at baseline as covariates and the different pharmacies as random effect. The effect of the intervention with the 95%-confidence intervals were calculated. For analyses of differences between the subgroups, interaction terms were calculated with the subgroup and the interaction between the subgroup and intervention included in the model.

Ethics and Confidentially

The Medical Ethics Review Committee of the Leiden University Medical Centre has considered the research proposal and concluded the Dutch Medical Research Involving Human Subjects Act (WMO) not applicable. The trial is registered at the Dutch National Trial Register (www.trialregister.nl) under the identifier NTR 5883. In addition, the study protocol was approved by the Institutional Review Board of UPPER, division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University. To protect the patients' identity, patients were assigned an unique study number. The signed informed consents are stored separately from the coded study data.

TABLE 1: Characteristics of included patients over the six months preceding the index date.

	Intervention (n=80)		Control (n=85)		p-value
Age (mean ± SD)	79.6	± 7.1	80.5	± 6.7	0.38 [a]
Female (n; %)	40	(50%)	41	(48%)	0.82 [b]
MDD system in use (n; %)	32	(40%)	29	(34%)	0.43 [b]
Cognitive impaired (n; %)	27	(35%)	20	(24%)	0.14 [b]
Frail (n; %)	41	(53%)	41	(53%)	1.00 [b]
VKA treatment indication atrial fibrillation (n; %)	72	(90%)	68	(80%)	0.07 [b]
TTR at baseline (mean ± SD)	59.5	± 15.5	56.9	± 17.2	0.30 [a]
Number of INR control visits (mean ± SD)	9.5	± 3.8	9.8	± 3.9	0.61 [a]
Number of INR measurements above 4.0 (n)	36		50		
Number of drugs (mean ± SD)	10.6	± 4.0	10.1	± 4.1	0.49 [b]

[a] Independent Students t-test
[b] Pearson Chi Square test
Missing values: Mini-Cog: n = 4; GFI: n = 11
Abbreviations: SD = standard deviation; MDD = multidose drug dispensing; TTR = Time in Therapeutic Range; INR = International Normalized Ratio; VKA vitamin K antagonist

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Results

From the 179 patients included in the RCT, 165 patients (92%) completed the six months study period and were included in the subgroup analyses. Baseline characteristics for intervention and control patients were similar at baseline (Table 1). The intervention resulted in an additional increase in TTR of 6.0% [95-CI: 0.29 – 11.71] (Figure 1).

In patients with a reduced MMC, the intervention resulted in an additional increase in TTR of 11.6% ($p < 0.01$) vs. -2.6% ($p = 0.56$) in patients with an adequate MMC. The difference between the subgroups was significant (p-value for interaction = 0.03).

In frail patients, patients older than 80 years and patients with a low self-reported adherence, the effect of the intervention tended to be stronger although the differences were not statistically significant. In frail patients, the intervention resulted in a 8.2% ($p = 0.04$) increase in TTR vs. a 0.5% ($p = 0.91$) increase among non-frail patients. In patients aged 80 years or older, the intervention resulted in an increase in TTR of 8.1% ($p = 0.05$) vs. 3.8% ($p = 0.37$) in patients aged between 65 – 80 years. In patients with a low self-reported adherence, the intervention resulted in an increase in TTR of 10.6% ($p = 0.06$) vs. a 3.1% ($p = 0.38$) increase in patients with adequate self-reported adherence.

No differences in effect of the intervention were observed for the subgroups based on gender, number of drugs, cognitive function and the patient's beliefs about VKA treatment. Sensitivity analyses with all 179 patients included resulted in similar effects of the subgroup analyses.

Discussion

This study showed that patients with a reduced MMC benefitted more from an MDD system compared to patients with an adequate MMC. Also the effect of the intervention tended to be stronger in frail patients, older patients and patients with a low self-reported medication adherence. However, the differences in the subgroups based on frailty, age and the self-reported adherence were not statistically significant. The patient's gender, cognitive function, number of drugs in use and the patient's beliefs about the VKA treatment did not appreciably affect the result of the intervention.

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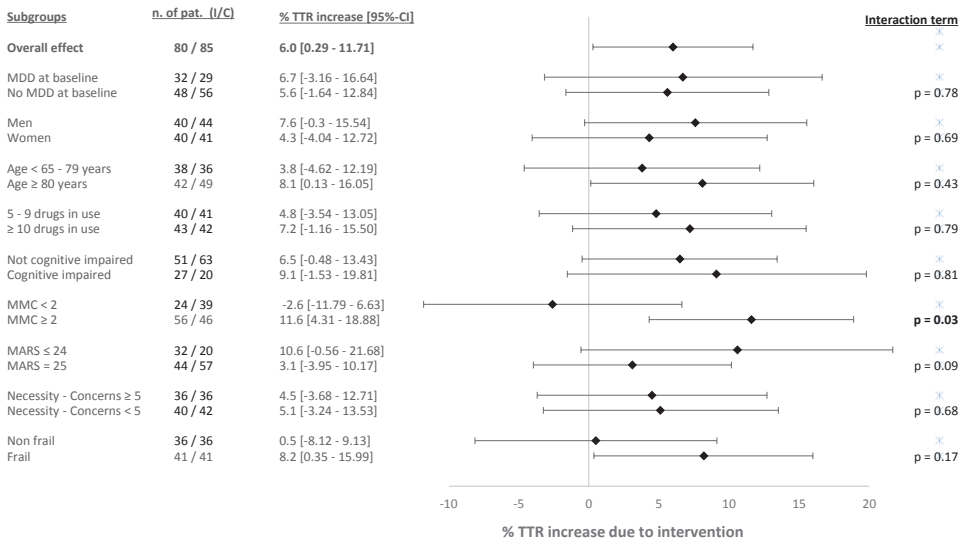

FIGURE 1: Subgroup and post hoc analyses. Statistical significant p-values are shown in bold.

Missing values: frailty n=11, cognition n=4, number of drugs n=12, necessity – concerns n=11.
Abbreviations: n. = number; pat. = patients; I/C = interventions / controls; TTR = time in therapeutic range; CI = confidence interval; MDD = multidose drug dispensing; p = p-value; MMC = medication management capacity; MARS = Medication Adherence Report Scale.

An MDD system will probably only improve the medication adherence, and thereby the TTR, if a patient was previously not able to adhere to the VKA dosing regimen. It was assumed that in patients aged over 65 years of age with polypharmacy, a low TTR was, at least partly, caused by a reduced MMC. This assumption was supported by the overall study results. In the subgroup of patients with a reduced MMC, the increase in TTR was significantly higher compared to patients with an adequate MMC. This suggests that identification of patients with a reduced MMC may be a sensible strategy in order to identify those patients who are most likely to benefit from the initiation of an MDD system.

One element of a patient's MMC is medication adherence. The patient's self-reported adherence was assessed using the MARS. Compared with adherent patients, the effect of the intervention tended to be stronger in patients with a low self-reported adherence (MARS ≤ 24). Using a different cut-off value of ≤ 23 to categorize patients as non-adherent did not influence the results (13.6% TTR increase among non-adherent patients vs. 4.1% increase among adherent patients). The MARS contains out of 5 questions and only one is related to unintentional non-adherence (*do you ever forget to take your VKA?*). Based on this one question, a TTR increase of 8.3% was observed in non-adherent patients vs.

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3.4% TTR increase in adherent patients. This suggests that the MARS may also serve as a strategy but that MDD system should mostly be used in unintentional non-adherent patients.

The majority of patients who start with an MDD system are assessed as frail or cognitively impaired.[19] In theory, these patients could benefit from an MDD system. For instance, a patient with a cognitive impairment is unlikely to complete a complex task like his medication management. VKAs can be especially difficult as the daily dose can fluctuate. The increase in TTR did not differ in the subgroups based on the patient's cognition. However, patients who were assessed as frail tended to benefit more than non-frail patients. This difference was independent of the patient's age and cognitive function. Another important determinant was the patient's age. The effect of the intervention tended to be stronger among patients ≥ 80 years of age compared with patients who are 65 – 79 years of age. The use of an MDD system tended to have a stronger effect in patients ≥ 80 years of age or who were assessed as frail. As a reduced MMC is correlated with age and frailty, it is recommended to screen patients over 80 years of age and frail patients on their MMC.

The patient's beliefs about his VKA treatment did not influence the effect of the intervention. Patients using VKAs are under strict supervision of anticoagulation clinics. One important element of the treatment is extensive counselling. Possibly, the extensive counselling decreases the patient's concerns and increases the patient's needs about VKA treatment. In almost all patients (84%), the necessity for the use of VKA treatment outweighed the concerns. In addition, patients with more concerns are theoretically intentionally non-adherent. It is unlikely that the initiation of an MDD system will influence their concerns and thereby affect the TTR.

Users of 10 or more drugs did not benefit appreciably more from the use of MDD systems than patients who used 5-9 drugs. Although the use of a high number of drugs is associated with a reduced medication adherence. However, the fact that all patients already used at least five chronic drugs may have limited the risk on even a lower medication adherence.[22-24]

Our study had several strengths. First, the included patients had similar characteristics of patients who use MDD systems in daily clinical practice. Patients were old, frail or cognitively impaired. These characteristics match with an earlier study among patients who were about to start with an MDD system.[19] Second, the used outcome, the patient's TTR, is an objective measurement based on multiple INR assessments. Thereby, the TTR reflects the quality of anticoagulation over a six months period. In addition, the TTR is

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strongly correlated with clinical outcomes like bleeding and thromboembolic events. An improvement in TTR will result in a lower number of bleedings and thromboembolic events.

This subgroup analysis also had some limitations. Most importantly, the original RCT was not designed to show significant differences between the different subgroups presented in this study. However, we deliberately collected baseline characteristics to enable more in-depth subgroup analyses. The results are therefore primarily intended to generate hypotheses for which patients the use of MDD systems is most likely to be effective. For conclusive evidence more studies in selected patient groups are needed, ideally with outcomes related to different morbidities. Second, only patients were included in the subgroup analyses who completed the full six months study period as intended. The outcome, an increase in TTR, is a continuous variable based on the patient's INR measurements. For the calculation of a TTR, a minimum of two INR measurements are needed. However, a TTR based on only two INR measurements is much less robust compared with a TTR based on six months with numerous INR measurements. To eliminate the potential bias, only patients were included who completed the study as intended. However, less than 10% of the originally included patients were not included in this analysis and sensitivity analyses with all 179 patients did show comparable results.

Conclusion

An MDD system was especially effective to increase the TTR among patients with a reduced medication management capacity. This emphasises the importance to identify patients with a reduced MMC. Its recommended to periodically screen old and frail patients on their MMC as these patients tended to benefit from an MDD system. If indeed patients have a reduced MMC, the initiation of an MDD system can be an effective strategy to support these patients with their medication regimen.

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Declarations

Ethics approval and consent to participate:

The Medical Ethics Review Committee of the Leiden University Medical Centre has considered the research proposal and concluded the Dutch Medical Research Involving Human Subjects Act (WMO) not applicable. In addition the study protocol was approved by the Institutional Review Board of UPPER, division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University. Patients gave written informed consent.

Competing interest

B. Mertens received an unconditional grant for the PhD project about multidose drug dispensing to conduct this research.

Funding

This study was performed as part of a larger PhD project on multidose drug dispensing. The project received unrestricted funding from The Royal Dutch Pharmacists Association and from a conjunction of six MDD suppliers (SPITS BV, Apotheek Voorzorg BV, Verpakapotheek, Pluripack, 5 Sterrenapotheek, Brocacef Maatmedicatie BV) in the Netherlands. All intellectual and publication rights are reserved for the investigators.

Authors' contributions

BM, HFK, RvM, FvdM and MB were responsible for the study concept and design. BM drafted the initial version of the manuscript. All authors contributed to the writing of the manuscript and approve the final manuscript for submission.

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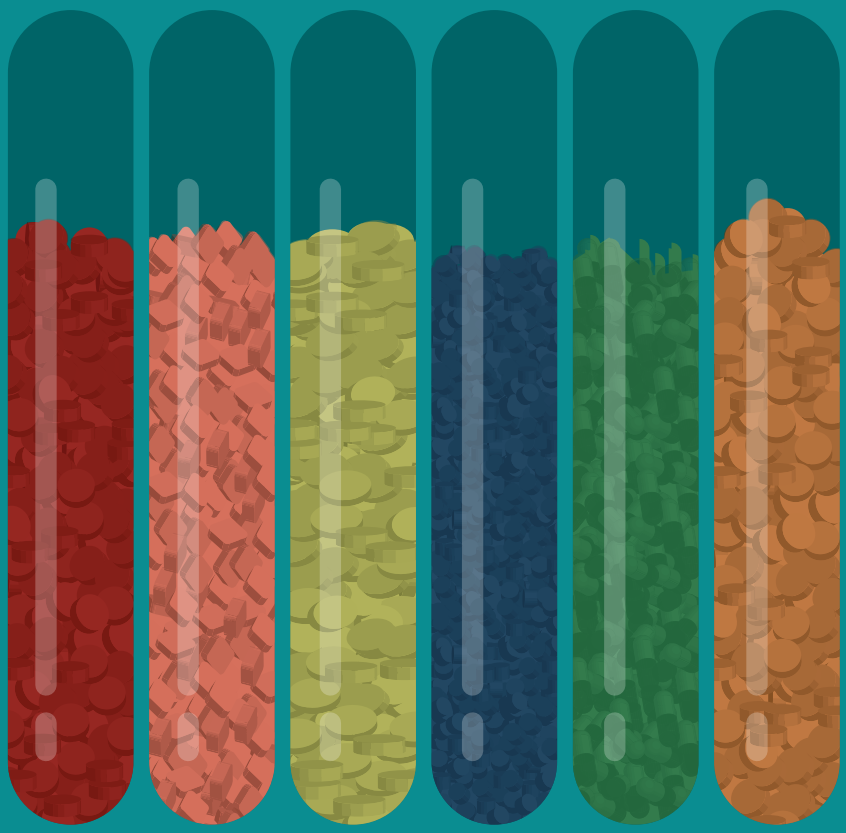

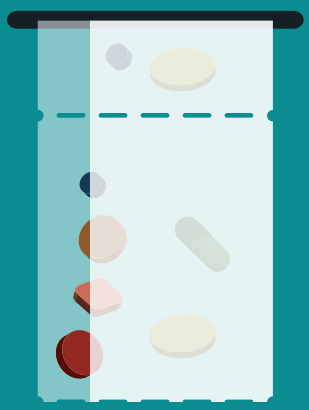

Chapter 9

General discussion

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GENERAL DISCUSSSION

Due to the ageing of the population and improved medical treatment options, the number of patients with multimorbidity and polypharmacy will continue to increase over the next several decades.[1,2] Under the influence of governmental policy, the emphasis of long-term care has shifted from institutionalised care to primary care.[3] As a consequence, the complexity of patients in primary care is increasing. In order to deliver high quality and efficient care to these complex patients, a multidisciplinary approach that involves prescribers, home care and community pharmacists is required.

From a pharmacist's perspective, a major challenge is the patients' medication management. Due to multimorbidity and improved medical treatment options, patients use an increasing number of drugs with complex dosing regimens.[4] Due to ageing and multimorbidity, patients experience a range of functional problems (e.g., cognitive impairment, impaired manual dexterity, and impaired vision). This causes patients to gradually lose their ability to manage their own medication. Automated multidose drug dispensing (MDD) systems can help patients who have lost their medication management capacity (MMC).[5-9]

In the Netherlands, 500,000 patients received their drugs via an MDD system in 2017.[10] The proportion of patients who use MDD systems increases with age; among patients above 80 years of age, 25% receive their medication via an MDD system.[11] Despite the widespread use of MDD systems, evidence for the benefits of MDD is scarce.[8,9,12] This thesis presents different studies that focused on the use of MDD systems in community-dwelling older patients, in which we aimed to answer the three following research questions: (1) which patients should be selected for the use of an MDD system, (2) how should the pharmaceutical care around MDD patients be optimised and (3) what are the effects of an MDD system on different outcomes.

Main findings of this thesis

- In Chapter 2, we compared the characteristics of patients who were about to start with an MDD system with control patients. The majority of patients who were about to start using MDD systems had multiple medication management problems, indicating a reduced MMC. A large proportion of patients who were to start using an MDD system were assessed as frail (60%), or suffered from cognitive impairment (40%). A minority of patients had a small number of medication management problems, indicating overuse of the MDD system. In contrast, a small proportion of control patients had numerous medication management problems, indicating the potential need for an MDD system.

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- In Chapter 3, the medication patterns of patients who initiated an MDD system were explored using a longitudinal study design. Patients who had started to use an MDD system differed from matched control patients, as they already used more drugs and more potentially inappropriate medications (PIMs) months before the initiation of the MDD system. The number of drugs and PIMs gradually increased until the initiation of the MDD system, after which the number of drugs and PIMs were higher, but stable.
- Chapter 4 presented the results of a survey of current users of an MDD system. The initiation of an MDD system was mostly a shared decision between the patients and health care professionals. The vast majority of patients indicated that the initiation of an MDD system supported them with their medication use. Readability of the printed text and difficulty in opening the pouches were disadvantages that can be improved.
- Chapter 5 was an observational study that described the process of drug regimen changes in the MDD system. Half of the adjustments to MDD systems were effectuated immediately. Pharmacists estimated that 27% of the immediate adjustments were unnecessary immediate effectuated. Immediate drug regimen changes were time consuming, especially for pharmacy technicians.
- In Chapter 6, we presented the study protocol of a randomized controlled trial (RCT) that assessed the effect of MDD systems on the time in therapeutic range (TTR) in patients using vitamin K antagonists.
- In Chapter 7, the results of the RCT were described. Dispensing vitamin K antagonists (VKAs) via an MDD system proved to be an effective strategy to improve the quality of anticoagulation.
- Chapter 8 was an explorative subgroup analysis of this RCT. Patients with a reduced MMC benefitted more from an MDD system compared to patients with an appropriate MMC. In addition, the effect of the intervention tended to be stronger in patients aged 80 years and older, frail patients, or patients that were non-adherent to VKA therapy. The patient's gender, cognition, beliefs about VKA treatment, or the number of drugs did not influence the effect of MDD.

In this final chapter, the implications of our findings are framed in a broader context by discussing how to select the appropriate patients for an MDD system, how to optimise the pharmaceutical care for patients with an MDD system, and how to measure the effects of MDD systems in future research.

This chapters finishes with recommendations for future research and clinical practice.

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Which patients should be selected for the use of an MDD system?

The current Dutch guideline for dosing aids in clinical practice states that patients with a reduced MMC are eligible for an MDD system.[5] However, an unambiguous definition of a reduced medication management capacity has not yet been provided. In practice, this leads to the situation in which MDD systems are initiated based on the 'expert opinions' of the physician and pharmacist, whereby health care professionals must balance the advantages (patient's self-efficacy, improved MMC and medication safety) and disadvantages (costs, risk of patronising the patient, loss of independence) of an MDD system.

Medication Management Capacity

The patient's MMC is a broad concept extensively described in **Chapter 1.** In the past, various screening tools have been developed to determine patients' MMC, but none met our requirements.[13,14] Therefore, we developed two versions of a questionnaire that aimed to assess patients' MMC. The first questionnaire was a comprehensive questionnaire based on the patients' medication regimen and included questions that covered the different domains of the patient's MMC.[15-19] It included 22 potential problems and 11 questions with regard to the patients' characteristics. The questionnaire distinguished patients with a reduced MMC from patients with an adequate MMC **(Chapter 2)**. The patients' perceived problems were divided over the four domains, but none of the domains were solely predictive for a reduced MMC.

The majority of patients who were about to start to use an MDD system had six or more potential medication management problems, which suggests a reduced MMC. This was endorsed by the patients themselves: 70% were of the opinion that they had lost the ability to manage their own medication. We therefore conclude that even without strict criteria, health care professionals have a fairly accurate estimation of patients' MMC. However, there is room for improvement.

Approximately 30% of the patients had less than six potential medication management problems. In these patients, the initiation of an MDD system is questionable. When explicitly asked, only 34% of these patients were of the opinion that they had lost their MMC. In the survey of current users of an MDD system **(Chapter 4)**, 19% of the patients indicated that the MDD system was primarily initiated for their convenience. It can therefore be concluded that there is some overuse of MDD systems. However, and possibly more alarming, 7% of all patients who used manually dispensed medication

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had six or more potential medication management problems and indicated to have lost the ability to manage their medication **(Chapter 2)**. Clearly, these patients are in need of help with their medication. In addition, 15% of the control patients had six or more potential medication management problems but indicated to be able to manage their medication regimens themselves.

For the RCT, we abbreviated the first questionnaire to make it easier to apply. From each of the four domains, the question that was most correlated with a reduced MMC was included in the new questionnaire. Two additional questions that we estimated to be important for the patient's MMC were also included. The first additional question was '*Does the patient experience problems with the packaging of the medication?*' (functional). A problem with the outer packaging of medication can hamper the use of medication, and might be overcome with the initiation of an MDD system. The second question was '*can the patient recall the correct indication for > 75% of their medication?*' (medication knowledge). This question was included as it was correlated with a reduced MMC in an explorative multivariate analysis and associated with the use of an MDD system in a study by Kwint et al.[20] These six questions were supplemented with the patient's own estimation of his MMC and two questions that were related to the patient's home situation. In the subgroup analysis of the RCT, patients were stratified into two groups based on their median scores on this MMC questionnaire **(Chapter 8)**. Patients with two or more MMC problems benefitted more from the initiation of an MDD.

Which risk-factors are associated with a reduced medication management capacity?

Advanced age has been associated with a reduced MMC.[14] This can be explained by the fact that as patients age, their health status slowly deteriorates, and they begin to experience problems with their vision, manual dexterity and cognition.[21,22] Concurrently, the prevalence of diseases such as Parkinson disease and arthritis increase, which can impede patients' appropriate use of their medication.[23,24] In general, patients with a reduced MMC were older compared to the control patients **(Chapter 2)**. The high prevalence of MDD use among older patients is exemplified in the database study, in which not all identified MDD users could be matched with a control patient, as most of the very old patients already received their medication via an MDD system **(Chapter 3)**.[11] The MDD system's potential to be especially beneficial for patients over 80 years of age was demonstrated in the subgroup analysis of the RCT **(Chapter 8)**. The effect of the initiation of an MDD system tended to be stronger in patients over 80 years of age compared to younger patients. From all three studies, it can be concluded that the patient's age is a risk factor associated with a reduced MMC.

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A notable overrepresented group in our studies were frail patients **(Chapter 2** and **Chapter 7)**. It is estimated that approximately 25% of the community-dwelling older population is frail, depending on the criteria used, but approximately two thirds of the patients who were about to start using an MDD system were classified as frail using the Groningen Frailty Indicator (GFI) **(Chapter 2)**.[25] This suggests that frailty is associated with a reduced MMC. This hypothesis was supported by our findings in the subgroup analysis of the RCT **(Chapter 8)**, in which there was a distinctive difference in the subgroups based on frailty (8.1% versus 0.5%).

Another frequently suggested risk factor for a reduced MMC is the patient's cognition.[7,20,26,27] A patient with cognitive impairment is unlikely to accurately complete a complex task, such as medication management. With the use of an MDD system, the appropriate execution of the patient's drug regimen may be facilitated. In line with frailty, the prevalence of cognitively impaired patients was high (40%) among patients who were about to start using an MDD system **(Chapter 2)**, but in contrast with the subgroups based on frailty, the difference between the subgroups based on cognition was minimal **(Chapter 8)**. One explanation for this could be that patients with a cognitive impairment might forget to take their medication, irrespective of how it is dispensed; MDD systems may not necessarily be a solution for these patients.[28] Patients' cognitive ability is expected to gradually decline over time, and with this decline, patients experience a variety of problems in daily life that are not only related to their medication management. Screening of patients' MMC is therefore warranted, but a screening with a much wider scope should be performed.

A frequently used criterion for eligibility for an MDD system is polypharmacy. With an increasing number of drugs, it is assumed that a patient has an increasing risk to suffer from a reduced MMC. However, in the performed subgroup analyses, there was no difference between the groups based on the number of drugs **(Chapter 8)**. As a consequence, we advise that the number of drugs should not be used as an explicit criterion.

In conclusion, patients with a reduced MMC indeed benefit from an MDD system. Patients who are over 80 years of age and those who are frail are especially at risk to suffer from a reduced MMC. Therefore, these patients should be periodically screened with regard to their MMC. We developed a questionnaire based on patients' daily routines that can be used to screen patients on their MMC. The short version can be conducted in approximately 10 minutes and seems therefore to be more suitable than the extended version. Explicitly, the questionnaire must not be considered to be a checklist; it should be used as a screening tool. Patients can require an MDD system even though they

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experience only one of the problems identified by the questionnaire. Ultimately, the initiation of an MDD system should be based on a shared decision between the patient and the health care professional.

How should the pharmaceutical care around MDD be optimised?

As a consequence of the shift of institutionalised care to community care, the complexity of the patients in primary care is increasing.[29] From 2025, the rise in the number of patients who are over 80 years of age will accelerate (the double ageing effect).[1] These patients will require even more attention from health care professionals, as they suffer from multimorbidity and have the highest risk for medication-related hospital admissions.[30,31] However, health care professionals' available time is limited, and GPs have already expressed their concerns about their increasing workload.[32] Simultaneously, community pharmacists are in a transitional phase from logistics to health care providers.[33] Pharmaceutical care for this specific group of patients can be divided into three areas: the identification of patients with a reduced MMC, the pharmaceutical care for current users of an MDD system, and the conditions required for the pharmacists to provide the most efficient and effective care. To cope with the challenges associated with the ageing of the population and increasing use of MDD systems, pharmacists, patients, prescribers and home carers must collaborate to optimise the pharmaceutical care around users of MDD systems.

Implementation of screening on medication management capacity

As suggested, patients who are over 80 years of age, and frail patients who use manually dispensed medication should be periodically screened on their MMC. With increasing numbers of patients, this might be a challenge and requires coordinated care.

An obvious location to screen patients on their MMC is the community pharmacy. Electronic repeat dispensing services are implemented on a large scale in primary care. In these services, the patient's chronic medication is synchronised and dispensed at the same moment. At present, this is primarily a logistical process for the purpose of efficiency for the patient and the pharmacy, but ideally, it is combined with a regular evaluation of the patient's pharmacotherapy. Once a year, pharmacy technicians can screen patients on their MMC. A major advantage is that all chronic drugs are dispensed concomitantly and are thereby available in the pharmacy. This enables the patient to demonstrate his MMC with the use of his own medication regimen.

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Next to community pharmacists, prescribers and practice nurses will probably observe signs of a reduced MMC. At many places, integrated care programmes for frail and elderly patients are being implemented. Within these programmes, patients are screened on frailty or cognitive function. If a patient who uses manually dispensed medication is identified as frail or cognitively impaired, a screening on his MMC is advisable. Within these integrated care programmes, agreements can be made with regard to who is responsible for the screening.

Most patients visit the pharmacy or their physician, but patients are also visited in their homes by home care workers. During these visits, home care workers may detect signs of medication-related problems.[14] This has led to the development of the 'Home Observation of Medication related problems by homecare Employees' (HOME) instrument. Unfortunately, this information is rarely shared with pharmacists. The introduction of electronic registration systems for drug administration (e.g., NCare, Boomerweb, Medicheck) is an opportunity to improve the collaboration. Currently, these systems only facilitate one-way communication from the pharmacists to home care organisations. All of the information needed for the administration of the medication (e.g., patient information, patient medication, and administration time) is electronically sent from the pharmacy information system to the home care organisation. Home care employees can access patients' information using a mobile device, but pharmacists do not receive information about the patients' actual medication use or signals of potential medication-related problems. Therefore, the potential of electronic registration systems has not been fully utilised. If home care workers detect signs of a reduced MMC, pharmacists or technicians can visit the patient to screen the patients on their MMC, and a clinical medication review can be performed, if necessary.

Effectuation of drug regimen changes in the MDD system

Pharmacists have an extended responsibility to incorporate drug regimen changes in a patient's MDD system. Most patients with an MDD system have low medication knowledge **(Chapter 2** and **8)**, and can therefore not be expected to be able to identify a specific drug in an MDD system.[20] The provision of new medication that is separate from the MDD system can also be confusing for patients with a reduced MMC.[28,34,35] In addition, immediate adjustments of an MDD system are considered a high risk, as they are effectuated manually. Besides the associated risk, immediate drug regimen changes are time consuming compared to deferred adjustments **(Chapter 5)**. Therefore, immediate drug regimen changes should be avoided if appropriate. According to the participating pharmacists, one in four immediate drug regimen changes could have been deferred until the new MDD **(Chapter 5)**. There was a large difference in the proportion of

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immediate adjustments between pharmacies. This indicates that the proportion of immediately effectuated drug regimen changes can be influenced. The necessity of immediate adjustment cannot be decided based solely on the type of medication. For example, metoprolol can be initiated for blood pressure regulation (immediate adjustment not necessary) but also for cardiac arrhythmia (immediate adjustment necessary). Pharmacies with the lowest proportion of immediate adjustments indicated to have made clear agreements with prescribers. Ideally, prescribers denote the immediate necessity of a drug regimen change on the prescription, emphasising the importance of close collaboration between prescribers and pharmacists. By reducing the proportion of immediately effectuated drug regimen changes, the risk of medication errors decreases, and pharmacy technicians save time, which can be invested in the pharmaceutical care of patients (e.g., screening on MMC).

The application of clinical risk management among MDD patients

The use of clinical decision support systems (CDSS) is fully integrated in community practice.[36] Most triggers are generated by drug-drug interactions, drug-disease interactions or duplicate medication alerts. CDSS generate alerts after each dispensing of a drug, but as a consequence of the weekly or bi-weekly dispensing of MDD systems, the same alerts are generated every week or every two weeks. The large number of MDD users and the high average number of drugs per MDD user results in an excessive number of alerts. This increases the risk of alert fatigue and consequently the failure to respond to relevant alerts. To guarantee medication safety among MDD users, there is a need for the revision of the CDSS. Alerts should be clustered and change-based.[36] An alert must only be generated if there is a relevant change in the patient's situation (e.g., a new drug or laboratory test result, or a change in the patient's condition).

Evaluation between patient and pharmacist

Pharmacists normally counsel patients at the pharmacy counter or in a consulting room, but for the oldest patients, and especially frail patients who use an MDD system, medication is often delivered to the home. As a consequence, pharmacists might lose contact with these patients. The Dutch guideline for dosing aids recommends that patients' experiences with MDD systems are evaluated yearly.[5] In practice, this is often operationalised by sending a questionnaire to patients. This may not be the most appropriate approach. Firstly, it is likely that patients who use an MDD system because of limited MMC will have difficulty in understanding and completing a questionnaire. Secondly, the risk of socially desirable answers is considerable. The questionnaire aims to identify patients who, despite the use of an MDD system, perceive problems with their medication management. During face-to-face contact, verbal cues and non-verbal

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cues can be identified and anticipated, making face-to-face contact more suitable. We recommend that the use of the MDD system is evaluated in face-to-face meetings with patients at least once a year. This evaluation can be performed by pharmacy technicians, potentially with telehealth. However, not only the practical aspects of the MDD system should be evaluated; patients' drug therapy itself also requires regular attention.

Medication Review

In **Chapter 3**, we demonstrated that the number of drugs increased sharply around the initiation of an MDD system. Moreover, the number of PIMs increased at the start of an MDD. The sudden increase in the number of drugs and PIMs when starting the MDD system might be explained by the occurrence of a clinical event accompanied with a decrease in health status, the start of new medication and a decreased MMC. There are concerns that once an MDD has been started, all medication will be automatically repeated without evaluation.[37] Concurrently, the patient's health status will deteriorate slowly over time. The combination of polypharmacy and decreased health status warrants a regular critical review of the patient's medication. This is emphasised by the high number of drug-related problems identified in a clinical medication review among users of MDD systems.[38] At least once a year, a treatment review should be performed by the pharmacist in which the patient's actual medication use and data from the medical records is combined. This treatment review can be combined with the yearly evaluation of the MDD system by the pharmacy technician. If potential drug-related problems are identified, this treatment review could be expanded to a clinical medication review, including a patient interview. This is in line with the recommendations of the '*Vervolgonderzoek Medicatieveiligheid*' report to focus on high-risk patients and incorporate patients' medical clinical data.[31,39]

Reimbursement of MDD systems

Currently, the income of a pharmacy is mainly dependent on the reimbursement of logistics. Pharmacists have the possibility to provide pharmaceutical care which is reimbursed (e.g., medication reviews and inhalation instructions) but the opportunities are limited. This dependency on logistics might hamper implementation of the recommendations. For instance, it is recommended that pharmacists critically review patients' medication in order to decrease the number drugs and PIMs. However, if medication is ceased, this will result in a reduction of income for the pharmacy as a result of the provided care. As a consequence, some pharmacists may not perceive an incentive to deprescribe medication. Therefore, there is a high urgency to reorganise the reimbursement for community pharmacies with more emphasis on the reimbursement of care and not solely on logistics.

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What are the effects of an MDD system on different outcomes?

Little was known about the effects of MDD systems. Therefore, we explored the effects of MDD systems on a variety of outcomes, namely the effect on the patients' medication use **(Chapter 3)**, patients' experiences with MDD systems **(Chapter 4)** and the effect of MDD on patients' time in therapeutic range **(Chapter 7 and 8)**. In the next part, our findings are discussed together with suggestions for future.

Quality of drug treatment

MDD systems have been associated with a high use of PIMs.[40-43] We have shown that MDD systems are not themselves the cause of the increase in drugs and PIMs, but an MDD system is likely to be initiated because of a change in health status that is accompanied with an increase in the number of drugs **(Chapter 3)**. Based on the type of drugs initiated around the start of the MDD system (antithrombotic agents, analgesics and psycholeptics), patients probably experienced health events, such as a myocardial infarction, a bone fracture or delirium. Such an event might just cause these patients to lose their MMC. Undeniably, the number of drugs and PIMs was higher after the initiation of an MDD system. This calls for action.[44] The intention should not be to eliminate polypharmacy or the use of PIMs, but the pharmacotherapy should be appropriate. As already suggested, a treatment review – and, if needed, a clinical medication review – must be periodically performed.

As a consequence of the characteristics of MDD users, these patient are pre-eminently candidates for deprescribing of medication (e.g., blood pressure lowering medication, blood glucose lowering medication or statins). An additional advantage of MDD systems is the opportunity to taper patients' medication, which is sometimes necessary to avoid withdrawal symptoms (e.g., from antidepressants, benzodiazepines or opioids). A dose reduction can thereby be gradually effectuated and evaluated. The effect of medication reviews (with special attention to deprescribing) on patients' quality of drug treatment should be elaborated in the future.

Patient satisfaction and support of patients using MDD systems

MDD systems are mainly used to support patients with their medication use. Patient satisfaction and their experiences are therefore important to consider. Surprisingly, in two qualitative studies from the UK, patients had diverging opinions about the use of dosing aids.[28,35] The first group of patients felt that the use of dosing aids supported them in their medication use; with the use of the MDD system, patients were more

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autonomous. A second group of patients felt patronised because their independence was undermined; those patients were reluctant to use a dosing aid. In our study, this attitude was not observed. Almost all patients were very satisfied with the use of an MDD system **(Chapter 4)**, as it supported them in their use of medication. Only two patients were unsatisfied, although they declined the offer to return to the use of manually dispensed medication. This deviates from a survey performed in the UK, in which 35% of the users of MCAs preferred the use of manually dispensed drugs.[45] Remarkably, the initiation of the MDD system was not discussed with either of the unsatisfied patients in our study, whereas 78% of the satisfied patients reported that the initiation of the MDD system was discussed. This emphasises the importance of shared decision making. Before the initiation of the MDD system, patients must be counselled with regard to their expectations and wishes.

Limited research was aimed at the patients' experiences with MDD systems. As indicated by the patients themselves, the legibility of the printed text and the opening of MDD systems can be improved **(Chapter 4)**. Obviously, during the process of innovations and improvements to MDD systems, patients' preferences are of key importance and must be taken into account. But not only the patients' preferences in the practical aspects of MDD systems should be explored; the patients' preferences in pharmaceutical care are also of importance. For example, we recommend, if appropriate, that drug regimen changes should be deferred, although patients might have a different opinion about deferred drug regimen changes.

Intermediate outcomes

Despite the widespread use of MDD systems and a general belief among health care providers that people with a reduced MMC benefit from MDD systems, there is limited scientific evidence for the effectiveness of MDD systems (and other dosing aids).[28,46] Ideally, the effect of an MDD system is assessed on clinical outcomes, such as mortality, morbidity and hospital (re)admissions, but to demonstrate the effect of an intervention that is primarily aimed at improving adherence to such clinical outcomes, long lasting studies with a high number of patients would be needed. In addition, it may be difficult to find an appropriate control group, as it may be unethical to assign patients with an obviously low MMC to a control group that does not receive MDD. It is therefore unlikely that such studies will ever be conducted.

In our performed RCT **(Chapter 7)**, dispensing vitamin K antagonists via an MDD system improved patients' TTR. The results indicate that the initiation of an MDD system supports patients in their medication use. However, the effect of the intervention was modest. Therefore, we performed a subgroup analysis to identify patients that benefitted

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most from the intervention **(Chapter 8)**. This subgroup analysis showed that patients with a reduced MMC benefitted most from the initiation of an MDD system; a result that was supported by the performed survey among current users of MDD systems **(Chapter 4)**. Patients indicated that the use of MDD systems indeed improved their medication use.[34] Still, more studies into the benefits of MDD with different outcomes related to other morbidities are needed.

A Cochrane review and meta-analysis assessed the effect of reminder packaging for improving adherence to self-administered long-term medication.[9] Twelve studies were included that used only a dosing aid as intervention, all included studies used MCAs, and four studies determined the effect on medication adherence. Overall, a positive effect on the percentage of pills taken in the MCA groups was observed, with an increase of 11%. Two trials provided data on the patients' self-reported adherence, but the use of MCAs did not affect the self-reported adherence. It must be noted that assessing the effect of an MDD system on the patients' medication adherence is almost impossible because of the automatic repeating character of MDD systems. However, the use of new technologies might facilitate the possibility to investigate the effect of MDD systems on medication adherence. Examples are the use of the Medido, Pillo or chips with Near Field Communication (NFC) techniques.[47,48] In the future, tiny electronic circuits may be printed on or attached to the pouches.

Regardless, optimal medication adherence is not the ultimate goal of the initiation of an MDD system; the overall goal is to improve patients' health. As a consequence, the effect of MDD systems on clinical outcomes is of more interest. In the same Cochrane review, two studies assessed the effect of dispensing medication via a dosing aid on HbA1c levels.[9] The application of MCAs reduced HbA1c levels by 0.7% mmol/mol, which is an effect size that is comparable to the addition of a second or third oral antidiabetic in a patient with type 2 diabetes. However, this effect on HbA1c was driven by one study. For the effects on patients' blood pressure, two studies were included in the meta-analysis. A non-significant reduction in the systolic blood pressure was observed while a significant 6 mmHg reduction was identified in the diastolic blood pressure. Remarkably, most studies were performed in a middle-aged and relatively healthy population. It is less obvious that these patients suffered from a reduced MMC. An unambiguous effect of an MCA on intermediate outcomes in these patients is therefore not expected. Studies into the effects of dosing aids must include patients who are old, frail and/or have a reduced MMC.

Finding an appropriate and objective clinical outcome for studies using MDD is a challenge. We considered many intermediate outcomes before we decided to use the

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TTR. An obvious and frequently recommended outcome would be the patient's blood pressure.[9] A high blood pressure is treated with a combination of antihypertensive drugs. The more drugs that a patient uses, the higher the probability that the patient will be non-adherent to his medication regimen.[49,50] In such patients, an MDD system might be an effective strategy to improve their blood pressure. However, in the oldest patients, different blood pressure target ranges are regarded as appropriate. In addition, the quality of life could be of higher importance than reaching target goals for blood pressure. Determining the effect on the average blood pressure reduction would be inappropriate. The patient's HbA1c is another example of an objective outcome measure with different target ranges between patients. It has been shown that dosing aids can positively affect HbA1c levels, but individualised HbA1c target ranges have been introduced that depend on the duration of the diabetes, the patient's age and therapy.[51] In addition, LDL treatment target ranges differ. Statins are frequently deprescribed in patients who are old or frail; exactly the patients who are potential candidates for an MDD system. These limitations could be overcome by the use of personal treatment goals. The outcome would not be the average reduction of a measurement, but the achievement of a predefined treatment goal. A second aspect that must be taken into account when using outcomes such as blood pressure, HbA1c or LDL is the frequency of the monitoring. In practice, these outcomes are performed once a year. To monitor the effect of an intervention, more measurements are likely needed. Increasing the number of control visits and monitoring is in itself an intervention that might affect the adherence in the control group, and thereby the outcome.

The effect of MDD systems could also be explored with the use of database studies. Big data enables researchers to combine data from different sources (e.g., hospitals, general practices and pharmacies). We had planned to explore the effect of the initiation of an MDD system in diabetes patients on HbA1c and cholesterol levels, but after conducting our longitudinal database study, we realised that database studies with matched controls are more complicated than initially perceived, due to potential sources of bias. Firstly, patients who will start to use an MDD system differ from their matched control patients long before the initiation of an MDD system. Secondly, upon the initiation of an MDD system, a non-negligible proportion of patients experienced a clinical event. Thirdly, with the initiation of the MDD system, more antipsychotics were prescribed. Antipsychotics are known for their metabolic effect, negatively influencing the patient's HbA1c or cholesterol levels. In addition, the outcome in a nested case-control study may be biased. Concurrently, the clinical event might have caused the initiation of an MDD system but also affect the outcome.

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In conclusion, more studies that assess the effect of MDD systems are warranted. While we demonstrated the effect of MDD systems on a specific outcome in users of vitamin K antagonists, this effect must be confirmed with various outcomes related to different morbidities. Both RCTs and database studies might be appropriate research designs, although it can be challenging to find an outcome that can objectively determine the effect of an MDD system.

Additional topics for further research on MDD systems?

In this thesis, we focused on older patients with polypharmacy who lived in the community. However, MDD systems are used in a variety of settings which have not been included in our studies. In this last part, different opportunities and challenges associated with the use of MDD systems that require further research are discussed.

MDD systems for specific groups of patients

In this thesis, we focused on the older patients with polypharmacy, but MDD systems are also frequently applied in patients with psychiatric disorders, or in those with functional disabilities. MDD systems are applied to these patients for two reasons. Firstly, these patients can be disorganised due to their psychiatric disorders, and with the use of an MDD system, their medication regimen is clearly structured. Secondly, in those who are supported by professional care for the administration of their medication, legislation stipulates that medication must be dispensed via a dosing aid. Among patients with psychiatric disorders, treatment with psycholeptics and psychoanaleptics is sometimes continued for too long, especially in the absence of schizophrenia. Due to the automatic repeating of medication in an MDD system, this problem may potentially increase. Therefore, pharmacists and physicians should be especially alert to the use of psycholeptics and psychoanaleptics in these patients.

In contrast to the challenges among these patients, there are also opportunities. As these patients frequently use medication that is subject to therapeutic drug monitoring (e.g., lithium, clozapine and valproic acid), the application of MDD systems enables close follow-up of these patients, both for clinical practice and research. Tapering of medication can also be facilitated with the use of MDD in these patients, potentially increasing the success rate of drug discontinuation.

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Costs effectiveness of MDD systems

In general, the expenditure on health care is continuously rising. It is therefore important to evaluate the economic impact of any new health care intervention. The use of MDD systems may enable patients to continue to live in the community independently without home care. Moreover, the use of MDD systems may reduce clinical events (e.g., acute coronary syndromes or cerebral infarctions) due to improved efficacy of treatment. A disadvantage of the use of MDD systems is their significantly higher price compared to manual dispensing. Dispensing one drug via an MDD system costs an additional €100 per year compared to manual dispensing. With around 500,000 users, each of whom uses an average of six drugs, dispensing via an MDD system costs roughly €300 million per year more than by manual dispensing (500,000*6*100). However, these costs must be considered within context. The number of patients who live in nursing homes is decreasing, despite the ageing of the population.[3] Since 1998, the number of beds in nursing homes has been reduced by 29,000.[52] With the average cost of €200 per day per bed, a saving of around €2,117 million is realised each year.[53] The increase in the use of MDD systems in the past decade has likely contributed to the fact that patients can stay longer in their own homes. For a valid estimation of the costs and benefits of MDD, a formal health technology assessment (HTA) that incorporates all aspect associated with the use of MDD system should be performed. However, such an HTA would not be easy to perform, as a variety of health care professionals with different funding structures are involved in the care of patients.

As an example, we showed that the use of MDD systems improves patients' TTR, but have not studied its economic impact. Dispensing VKAs via an MDD system was costlier than via manual dispensing. However, not only the associated dispensing costs should be taken into account. On one hand, the incorporation of the fluctuating VKA regimens was time consuming, especially for pharmacy technicians. On the other hand, the intervention will result in a reduction of costs. By improving patients' TTR, the number of bleedings and thromboembolic events will be reduced, which are known to be costly. In addition, patients will require fewer INR assessments.

Health technology advantages

Recently, the Dutch Ministry of Health renewed its policy 'Longer at Home'.[3] Part of the new plan is an investment of €90 million in e-health innovations to support home dwelling patients.[54] Telemonitoring can reduce the risk of all-cause mortality and heart failure-related hospitalisations in patients with heart failure, a patient group that frequently uses MDD.[55] Users of MDD systems are predominantly patients who might also benefit from e-health. E-health interventions can be roughly divided into

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three categories. The first category is targeted at improving patients' self-management. MDD users have low medication knowledge **(Chapter 2)**; with the use of e-health, the patients' knowledge about medication may be improved in general, but more importantly in risky situations. Patients with an impaired kidney function are known to be at risk for medication-related hospital admissions. For these patients, it is important to temporarily cease or adjust medication, such as diuretics and RAS-inhibitors, during a heatwave or acute illness accompanied by fever, diarrhoea, or low fluid intake. Specific advice, and identification of the appropriate tablets can be incorporated into mobile applications. Secondly, telemonitoring can be used to improve communication between patients and health care professionals. Especially for patients who are unable to visit their GP or pharmacist, telemonitoring allows them to continue to maintain face-to-face contact. Technology may also facilitate the communication among health care providers, including GPs, pharmacists and home care workers. Lastly, smart medication dispensing devices such as the Medido or the Pillo offer additional functionalities, including automatic reminders to take the medication and web-based electronic monitoring of medication adherence by informal carers or health care providers.[47,48] More futuristic developments may be the incorporation of 3D-printed medication at the patient's home combined with continuous monitoring of the patient's vital functions. Based on the patient's measurements, the dose of the medication could be remotely adjusted to fit the patient's needs.

Pharmaceutical quality of medication dispensed via MDD systems

One important aspect that is receiving an increasing amount of attention is the pharmaceutical quality of the medication dispensed via MDD systems. Upon registration, pharmaceutical companies must demonstrate the pharmaceutical quality of the product during its shelf life, but in order to dispense the medication via an MDD system (or a dosing aid in general), the medication must be removed from its original packaging. As a consequence, the medication may be exposed to light, heat, air and humidity. All can negatively affect the pharmaceutical quality of the medication. One example is dabigatran, which has a limited shelf life of only six hours out of its original packaging.[56] This hampers the dispensing of dabigatran via MDD systems. Other drugs are also known to have a limited shelf life if dispensed via dosing aids.[57] Currently, a Swedish theory-based list is used to assess whether medication can be dispensed via an MDD system. Preferably, this theory-based list would be supported with scientific data. Ideally, an international open access database will be formed that incorporates all relevant information. In addition, to prevent new cases such as that of dabigatran, it is recommended that pharmaceutical companies demonstrate the pharmaceutical quality of newly registered products after also being removed from their original

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packaging. As dosing aids are dispensed for a maximum period of four weeks, data on the pharmaceutical quality over a period of six weeks out of the original packaging is recommended.

Sustainability

For the production of MDD systems, an estimated 237,000 kilos of plastic are used per year (500,000 users, an average of two pouches per day per patient, and 0.65 grams per pouch). The plastic pouches of MDD systems are made of non-biodegradable plastic, which is undesirable from an environmental perspective. Until now, the development of biodegradable pouches that meet the specific needs for MDD has proven to be very difficult. The plastic should simultaneously be thin, strong, printable, transparent, easy to open and should protect the medication from air and humidity. A different strategy to reduce the ecological impact of MDD systems would be to recycle the plastic pouches. This might be especially applicable in large nursing homes. However, privacy legislation complicates implementation. On the pouches, the patient's name and the name of the medication are printed. The plastic pouches are therefore destroyed and not recycled. In addition, pharmaceutical companies can help to reduce the ecological impact of MDD systems. In 2016, 1.1 billion tablets were dispensed via an MDD system. Of these tablets, 160 million had to be removed from their original packaging. Increasing the number of medicines available in large containers would decrease the waste of these packages.[58]

Conclusions

This thesis elaborated on the concept of patients' medication management capacity (MMC) and presented an array of studies that assessed the effects of MDD systems from different perspectives. To cope with the upcoming challenges of the ageing population and the likelihood that the use of MDD systems will further increase, action is needed on different levels to ensure continuous care for patients with an MDD system. Policy makers and health care funders should implement changes that stimulate pharmacists to provide more pharmaceutical care for this specific group of patients. More importantly, community pharmacists must act more proactively and collaborate with other health care professionals to improve the pharmaceutical care for this specific group of patients.

This leads to the following practical recommendations that require attention in the near future:

- To identify patients with a reduced medication management capacity in a timely manner, patients with polypharmacy over 80 years of age and frail patients must

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be screened on their MMC. In order to do so, community pharmacists should make clear agreements with prescribers, practice nurses and home care workers to identify and screen these high-risk patients.

- Before the initiation of the MDD system, patients must be counselled with regard to their expectations and wishes. The initiation of an MDD system must be a shared decision between the patient and health care professional. After the initiation of an MDD system, pharmacists and pharmacy technicians should maintain regular contact with the patient.
- Pharmacists and prescribers should make clear agreements regarding adjustments of MDD systems. Deferred adjustments should be default unless prescribers denote the immediate necessity of a drug regimen change on the prescription.
- At least once a year, a treatment review with particular attention on deprescribing should be performed by the pharmacist in which the patient's medication use and data from the medical records are combined.
- This treatment review can be combined with the yearly evaluation of the MDD system by a pharmacy technician. If potential drug-related problems are identified, this treatment review could be expanded to a clinical medication review, including a patient interview.
- To guarantee medication safety among MDD users, there is a need for the revision of the CDSS. An alert must only be generated if there is a relevant change in the patient's situation (e.g., a new drug or laboratory test result, or a change in the patient's condition).
- To stimulate pharmaceutical care for MDD patients, the reimbursement of community pharmacies must be reorganised. More emphasis must be placed on the reimbursement of care, and not solely on logistics.

In conclusion, despite the lack of robust evidence until now, MDD systems have been implemented on large scale over the past two decades. Health care professionals have a fairly good estimation of a patient's medication management capacity, but there is room for improvement. The findings in this thesis confirm the assumption that, if initiated, MDD systems supports patients in their medication use, especially those with a reduced medication management capacity.

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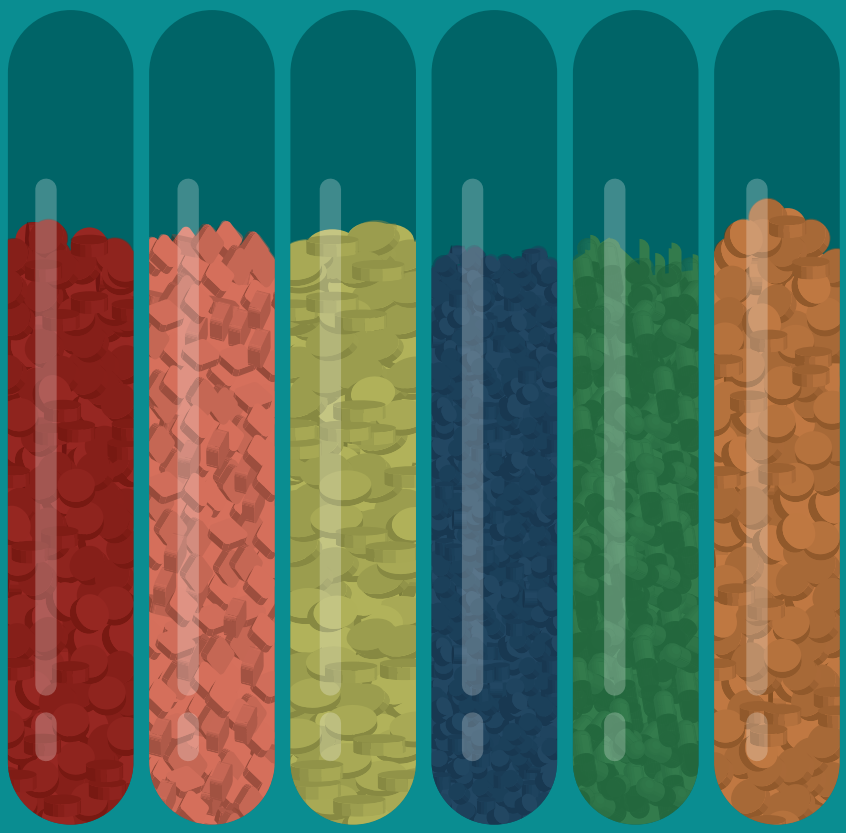

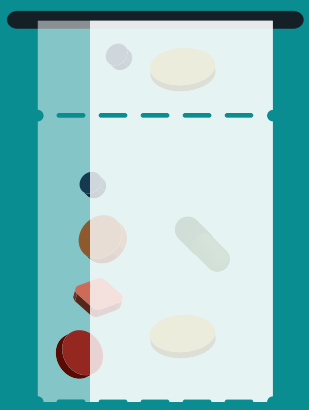

Appendices

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Summary

The number of patients with multimorbidity and polypharmacy will continue to increase over the next decades. From a pharmacist's perspective, a major challenge is the patients' medication management. Patients use an increasing number of drugs with complex dosing regimens. Due to ageing and multimorbidity, patients experience a range of functional problems (e.g., cognitive impairment, impaired manual dexterity and impaired vision). As a consequence, patients may gradually lose their ability to manage their own medication. Automated multidose drug dispensing (MDD) systems are used to support these patients with their medication management. It is assumed that dispensing the patient's medication via an MDD system will improve the appropriate use of medication which subsequently lead to better health outcomes. Despite the extensive use of MDD systems, evidence for the benefits of the use of MDD systems is scarce. In this thesis various studies are presented that were aimed to provide more insight in the use and effects of MDD systems in community care.

The studies presented in this thesis can be divided into two parts. In the first part, the initiation and use of MDD systems in daily clinical practice is explored from various perspectives. MDD systems are intended for patients with a reduced medication management capacity (MMC). However, an unambiguous description of a reduced MMC has not been given. Whether the appropriate patients receive an MDD system was therefore unknown. We aimed to answer this question in **Chapter 2** using a case-control study in which the experienced medication management problems of patients who were about to start with an MDD system were systematically documented and compared to control patients. Potential medication management problems were more prevalent among patients for who an MDD system was initiated compared to control patients. MDD patients were more likely to be assessed as frail or cognitively impaired. The majority of MDD patients (70%) had six or more potential medication management problems and were assumed to have a reduced MMC. In addition, 70% of these patients also indicated themselves to have lost their MMC. On the other hand, 30% of the MDD patients had only five or less potential medication management problems and only one third of these patients indicated themselves to have lost their MMC. Among these patients the initiation of MDD systems may be unnecessary. Oppositely, underuse of MDD system was observed as well. 22% of the control patients had six or more potential medication management problems. In addition, 30% of these patients indicated themselves to have lost the ability to manage their medication. To timely identify patients who may benefit from MDD systems, it's advised that healthcare professionals screen older patients with polypharmacy on their MMC.

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Despite intentions of improved patient care with MDD systems, epidemiologic studies suggest an association between the use of MDD systems and poor quality of drug treatment. In **Chapter 3** we performed a longitudinal cohort study which assessed the number of drugs in use and the prevalence of potential inappropriate medications (PIMs). We showed that patients who started with an MDD system differ from matched control patients, already months before the initiation of an MDD system. MDD patients used more drugs and more PIMs. Over time, the number of drugs and PIMs gradually increased and sharply peaked around the initiation of the MDD system. After the sharp increase, the number of drugs and prevalence of PIMs decreased slightly and stabilized. We concluded that the initiation of an MDD systems itself is not the cause of the increase in the number of drugs or PIMs, but presumably a change in the patient's health status causes an increase in number of drugs and PIMs. The combination of the deterioration of the patient's health status and increased number of drugs results in the initiation of an MDD system.

Qualitative studies in different countries among current users of dosing aids revealed divergent opinions from patients about the use of such systems. Some patients experience the use of a dosing aid as supportive for their independence, while others perceive a loss of independence. In **Chapter 4** we explored the patients' experiences of current users of MDD systems in the Netherlands. Our results deviated from the results of the earlier performed studies. In the Netherlands, patients are generally involved in the decision to initiate an MDD system. The start of an MDD system was discussed with the majority of patients (76%). The three main reasons for the initiation of an MDD system were a reduced MMC (50%), patient convenience (19%) and forgetfulness (15%). 90% of patients were of the opinion that the use of an MDD system supported them with their medication use and 76% indicated that the MDD system indeed improved their medication management. However, disadvantages were also reported. Especially, simplifying the manual opening of the bags and improving the legibility of the text on the pouches were addressed by patients. It can be concluded that for most patients the use of an MDD system seems appropriate. However, there are also patients for whom the use of an MDD system might be questionable as initiating an MDD system solely for patients' convenience is a relatively expensive solution and therefore assumed inappropriate.

The last study of the first part of the thesis **(Chapter 5)** was a cross-sectional study in which we examined how drug regimen changes in MDD systems were effectuated by community pharmacies. MDD guidelines recommend to defer drug regimen changes until the start of a new MDD system as manual immediate adjustment is a process with a high risk of dispensing errors. About half of all drug regimen changes were

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effectuated by immediate adjustment. Participating community pharmacists indicated that one third of these immediate drug regimen changes could have been effectuated by deferred adjustment. Especially cardiovascular medication and medication used in diabetes were more likely to be effectuated by immediate adjustment. Immediate drug regimen changes took twice as much time as a deferred adjustment. As a consequence of the higher risk and time needed for immediate drug regimen changes, deferred adjustments should be default unless prescribers denote the immediate necessity of a drug regimen change on the prescription.

In the second part of the thesis, the effect of the initiation of an MDD system in patients using vitamin K antagonists (VKAs) was assessed. In **Chapter 6**, the rationale and design of a randomised controlled trial (RCT) is described. VKAs are highly effective to treat and prevent thromboembolism. A disadvantage is the occurrence of bleedings. The risk of thromboembolism and bleedings is strongly associated with the time in therapeutic range (TTR). The lower the TTR, the higher the risk of thromboembolism and bleedings. The RCT assessed the effect of dispensing vitamin K antagonists (VKAs) via multidose drug dispensing on the patients' time in therapeutic range (TTR). We assumed that a low TTR (< 65%) was, at least partly, caused by a reduced medication adherence. Patients using VKAs over 65 years of age with a minimum of 5 chronic prescription drugs and a low TTR were randomised to the intervention group (dispensing all drugs via an MDD system) or control group (manual dispensing of VKA). The effect of the intervention was assessed after six months. For the analysis, a mixed-effects model was used with the intervention, MDD use at baseline, TTR in the preceding six months before the study period as covariates and participating pharmacies as random effect in the model.

The results of the RCT are presented in **Chapter 7**. A total of 179 patients were included. Mean TTR during the study was 79.2±18.0% in the intervention group and 72.5±20.1% in the control group. The intervention resulted in a 5.6% increase in TTR compared to the control group. An analysis with the patients who completed the study as intended (n= 108) resulted in a 8.3% increase in TTR compared to the control group. In addition to the increase in TTR in the intervention group, the time under the therapeutic range decreased in the intervention group compared with the control group. However, no differences were seen in the number of thromboembolic events which can be explained by the fact that the study was not powered to show these differences. These results suggest that the quality of anticoagulation treatment can be improved by dispensing VKAs via an MDD system, especially in patients with a TTR < 65%.

However, dispensing VKAs via an MDD system was not equally effective for all patients. Therefore, we performed subgroup analyses to identify specific groups of patients who

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benefit most from dispensing VKAs via an MDD system **(Chapter 8)**. The intervention was more effective in patients with two or more potential medication management problems (11.6% TTR increase) compared to patients with less than two medication management problems (2.6% TTR decrease). The effect of the intervention tended to result in a higher TTR increase in frail patients (8.2%) compared to non-frail patients (0.5%), in patients aged 80 years or older (8.1%) compared to patients aged 65 – 79 years (3.8%) and in patients with a low self-reported adherence (10.6%) compared to adherent patients (3.1%). The patient's gender, cognitive function, the number of drugs in use and patients' beliefs about VKA treatment did not appreciably affect the effect of the intervention. As a result, its recommended to periodically screen old and frail patients on their MMC. If these patients have a reduced MMC, the initiation of an MDD system can be an effective strategy to support their medication regimen.

Finally in **Chapter 9**, the implications of our findings were discussed in a broader context focussing on three questions. 1) Which patients should be selected for the use of an MDD system? 2) How to optimise the pharmaceutical care for patients with an MDD system? 3) How can the effects of MDD systems be measured in future research.

We showed that MDD systems are mostly initiated for patients with a reduced MMC. Patients who are over 80 years of age and those who are frail are more likely to suffer from a reduced MMC. Therefore the MMC of these patients should be periodically screened. Community pharmacists should make clear agreements with prescribers and home care workers to proactively identify and screen these high-risk patients. We developed a questionnaire based on patients' daily routines that can be used to screen patients on their MMC. The short version of this questionnaire might be suitable for use in daily clinical practice. Explicitly, this questionnaire must not be considered to be a checklist, it should be used as a screening tool. Ultimately, the initiation of an MDD system should be based on a shared decision between the patient and the health care professional.

In general, MDD patients suffer from multimorbidity, are old, and frequently frail or cognitively impaired. As a consequence, these patients have the highest risk for medication-related hospital admissions. Therefore, community pharmacists must be even more focused on the pharmaceutical care for these patients. After the initiation of an MDD system, pharmacists have an extended responsibility to incorporate drug regimen changes in a patient's MDD system. As immediate drug regimen changes are considered a high risk process and are time consuming, unnecessary immediate drug regimen change should be prevented. To minimise the number of inappropriate immediate drug regimen changes, the distinction between symptomatic treatment (immediate

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adjustment) and preventive treatment (deferred adjustment) might be helpful. Over time, it is expected that the patient's health status deteriorates. Therefore, pharmacists or pharmacists technicians should evaluate the use of MDD system periodically with patients in a face-to-face meeting. But not only the use of the MDD system should be evaluated, also the patients' medication must be reviewed with particular attention on deprescribing. To stimulate pharmaceutical care for MDD patients, the reimbursement of community pharmacies must be reorganised. In addition, to guarantee medication safety among MDD users, there is an urgent need for the revision of clinical decision support systems for MDD patients. An alert must only be generated if there is a relevant change in the patient's situation.

Despite the widespread use of MDD systems, there is limited scientific evidence for the benefits of MDD systems. We showed that MDD systems can positively affect the patient's TTR. But more studies that assess the effect of MDD systems on various outcomes are warranted. Both RCTs and database studies might be appropriate research designs, although it can be a challenge to find an outcome that can objectively determine the effect of an MDD system. Ultimately, a formal health technology assessment that incorporates all aspects associated with the use of MDD system should be performed.

In conclusion, this thesis presents an array of studies that assessed the use and effects of MDD systems from different perspectives. The findings in this thesis confirm the assumption that MDD systems can support patients with their medication use, especially those with a reduced medication management capacity. To cope with the upcoming challenges of the ageing population and the likelihood that the use of MDD systems will further increase, action is needed on different levels to ensure continuous care for patients with an MDD system. Policy makers and health care funders should implement changes that stimulate pharmacists to provide more pharmaceutical care for this specific group of patients. Even more important, community pharmacists should act more proactively and collaborate with other health care professionals to improve the pharmaceutical care for this specific group of patients.

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Samenvatting

De verwachting is dat het aantal patiënten met multimorbiditeit en polyfarmacie de komende decennia zal blijven toenemen. De meerderheid van deze patiënten wordt opgevangen in de eerstelijnsgezondheidszorg. Vanuit het perspectief van de openbaar apotheker is het medicatiebeheer van deze patiënten een uitdaging. Patiënten gebruiken steeds meer geneesmiddelen met complexe innameschema's. Met de toename van de leeftijd neemt de kans toe dat patiënten meer functionele problemen gaan ervaren (bijvoorbeeld cognitieve stoornissen, verminderde coördinatie of een verminderd gezichtsvermogen). Als gevolg hiervan zijn patiënten steeds minder in staat om hun eigen medicatie te beheren. Door het verstrekken van de medicatie via medicatie op rol wordt beoogd deze patiënten te ondersteunen met hun medicatiebeheer. Aangenomen wordt dat de toepassing van medicatie op rol het goed gebruik van geneesmiddelen zal bevorderen waardoor ook gezondheidsuitkomsten verbeteren. Ondanks de wijdverbreide toepassing van medicatie op rol, is de wetenschappelijke onderbouwing van het gebruik beperkt. Met de verschillende onderzoeken in dit proefschrift, is getracht meer inzicht te geven in de toepassing en het effect van medicatie op rol in de eerstelijnsgezondheidszorg.

Het proefschrift is onderverdeeld in twee delen. In het eerste deel is de toepassing van medicatie op rol beschreven vanuit verschillende perspectieven. Medicatie op rol is primair bedoeld voor patiënten met een ordeningsprobleem. Echter ontbreekt een eenduidige definitie of beschrijving van een ordeningsprobleem. Hierdoor is het onduidelijk of patiënten die starten met medicatie op rol inderdaad een ordeningsprobleem hebben. We hebben getracht deze vraag in **Hoofdstuk 2** te beantwoorden met behulp van een case-control studie. Potentiele medicatieproblemen van patiënten die op het punt stonden te beginnen met medicatie op rol werden systematisch gedocumenteerd en vergeleken met de potentiele problemen van controlepatiënten. Potentiële medicatieproblemen kwamen vaker voor bij patiënten voor wie medicatie op rol werd gestart. Startende medicatie op rol gebruikers waren tevens vaker kwetsbaar of hadden meer cognitieve problemen vergeleken met controlepatiënten. De meerderheid van de patiënten met een medicatie op rol (70%) had zes of meer potentiele medicatieproblemen waarmee verondersteld werd dat deze patiënten inderdaad een ordeningsprobleem hebben. Van deze patiënten gaf bovendien 70% zelf aan problemen met het beheer van hun geneesmiddelen te ervaren. Geconcludeerd kan worden dat deze patiënten inderdaad een indicatie hadden voor het starten van medicatie op rol. Echter voor 30% van de patiënten die starten met medicatie op rol is het minder duidelijk of zij echt een rol nodig hebben. Deze patiënten hadden vijf of minder potentiële medicatieproblemen. Van hen gaf

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slechts één derde zelf aan problemen met het beheer van geneesmiddelen te ervaren. Andersom kwam mogelijk ondergebruik van medicatie op rol ook voor, want 22% van de controle patiënten had zes of meer potentiële medicatieproblemen. Om patiënten met een ordeningsprobleem tijdig te identificeren wordt daarom geadviseerd oudere patiënten met polyfarmacie periodiek te screenen op mogelijke problemen met het medicatiebeheer.

Epidemiologische internationale studies suggereren een verband tussen het gebruik van medicatie op rol en een hoog aandeel potentieel ongewenste medicatie (PIM's). **Hoofdstuk 3** beschrijft een longitudinale cohortstudie waarin het aantal geneesmiddelen en de prevalentie van PIM's is beschreven. Patiënten die gestart waren met medicatie op rol verschilden van vergelijkbare controle patiënten, al maanden voor het starten van medicatie op rol. Medicatie op rol patiënten gebruikten meer medicijnen en meer PIM's. In aanloop naar de start van medicatie op rol nam het aantal geneesmiddelen en PIM's geleidelijk verder toe. Het gebruik ervan piekte scherp rondom het begin van medicatie op rol. Na deze sterke toename nam het aantal medicijnen en PIM's licht af om vervolgens te stabiliseren. Hieruit concluderen wij dat medicatie op rol niet de oorzaak is van de toename van het aantal medicijnen of PIM's. Het is meer aannemelijk dat een verandering in de gezondheidstoestand van de patiënt zorgt voor een toename van het aantal medicijnen en PIM's. De combinatie van de verslechtering van de gezondheidstoestand van de patiënt en het toegenomen aantal geneesmiddelen resulteert vervolgens in de start van medicatie op rol.

Uit verschillende kwalitatieve internationale onderzoeken onder huidige gebruikers van weekdoseersystemen bleek dat patiënten uiteenlopende ervaringen hebben met weekdoseersystemen. Een deel van de patiënten ervaart het gebruik van een weekdoseersysteem als hulp om onafhankelijk te blijven terwijl anderen juist een verlies van autonomie ervaren doordat het medicatiebeheer uit handen is genomen. In **Hoofdstuk 4** zijn de ervaringen van huidige gebruikers van medicatie op rol in Nederland onderzocht. De gevonden resultaten wijken af van de eerder uitgevoerde onderzoeken. Nederlandse gebruikers van medicatie op rol geven aan over het algemeen betrokken te zijn geweest bij de beslissing om te starten met medicatie op rol. De start werd besproken met de meerderheid van de patiënten (76%). De drie belangrijkste redenen voor het starten van medicatie op rol waren ordeningsproblemen (50%), gebruiksgemak voor de patiënt (19%) en vergeetachtigheid (15%). 90% was van mening dat medicatie op rol het medicatiebeheer ondersteunde en 76% gaf aan dat hun eigen medicatiebeheer was verbeterd. Patiënten gaven aan dat medicatie op rol verbeterd kan worden door de leesbaarheid van de tekst op de plastic zakjes te verbeteren en het openen van de plastic zakjes te vereenvoudigen. Geconcludeerd kan

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worden dat voor het overgrote deel van de patiënten het gebruik van medicatie op rol geïndiceerd is. Echter zijn er ook patiënten voor wie het gebruik van medicatie op rol twijfelachtig is aangezien enkel gebruiksgemak geen valide reden is voor het starten van medicatie op rol.

In het laatste onderzoek van het eerste deel van dit proefschrift **(Hoofdstuk 5)** is onderzocht hoe medicatiewijzigingen in medicatie op rol worden doorgevoerd door openbare apotheken. Wijzigingen kunnen worden doorgevoerd per volgende rol of middels acute handmatige aanpassing van de huidige rol. De KNMP richtlijn beveelt aan om dergelijke wijzigingen in de farmacotherapie zoveel mogelijk uit te stellen tot het begin van een nieuwe rol omdat bij handmatige aanpassing een hoog risico op fouten aanwezig is. De helft van alle medicatiewijzigingen werden echter acuut doorgevoerd. Opvallend was dat de deelnemende apothekers aangaven dat een derde van deze acute aanpassingen uitgesteld hadden kunnen worden tot het starten van een nieuwe rol. Met name wijzigingen in cardiovasculaire medicatie en diabetes medicatie werden vaker acuut doorgevoerd. Naast het hoge risico op fouten waren acute aanpassingen tevens erg tijdsintensief. Een acute aanpassing kostte twee keer zoveel tijd in vergelijking met een aanpassing per volgende rol. Wij adviseren daarom dat aanpassing bij voorkeur per volgende rol moet plaatsvinden, tenzij de aard van de wijziging acute aanpassing noodzakelijk maakt. Goede communicatie hierover tussen arts, apotheker en patiënt is hierbij essentieel.

In het tweede deel van dit proefschrift werd het effect van het starten van medicatie op rol op een objective gezondheidsuitkomst bepaald. In **Hoofdstuk 6** is de rationale en opzet van een gerandomiseerde gecontroleerde studie (RCT) beschreven. Vitamine K-antagonisten (VKA's) worden toegepast om trombose te behandelen en voorkomen. Een nadeel van VKA's is het optreden van bloedingen als gevolg van een doorgeschoten antistolling. Het risico hierop is sterk geassocieerd met de tijd dat een patiënt in de therapeutische range (TTR) is ingesteld. Hoe lager de TTR, hoe hoger het risico op trombose en bloedingen. Binnen de RCT is onderzocht of door het verstrekken van VKA's via medicatie op rol de TTR verbeterd kon worden. Hiervoor werden patiënten met een lage TTR (<65%) geïncludeerd. Er werd verondersteld dat een lage TTR, althans gedeeltelijk, werd veroorzaakt door een verminderde therapietrouw van VKA's. Patiënten ouder dan 65 jaar, chronische gebruikers van VKA's en die 5 of meer geneesmiddelen gebruikten, werden gerandomiseerd naar de interventiegroep (waarbij alle geneesmiddelen via medicatie op rol werden verstrekt) of controlegroep (waarbij de VKA via een reguliere medicijnverpakking werd verstrekt). Na een studieperiode van zes maanden werd het effect van de interventie beoordeeld met de TTR als primaire uitkomstmaat.

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De resultaten van de RCT staan beschreven in **Hoofdstuk 7**. In totaal zijn 179 patiënten geïncludeerd. De gemiddelde TTR tijdens het onderzoek was 79.2 ± 18.0% in de interventiegroep en 72.5 ± 20.1% in de controlegroep. De interventie resulteerde in een toename van de TTR met 5.6% in vergelijking met de controlegroep. Een analyse met de patiënten die de onderzoeksperiode voltooiden zoals bedoeld (n = 108) resulteerde in een toename van 8.3% in vergelijking met de controlegroep. Het verschil in TTR leidde in de relatief korte onderzoeksperiode van het onderzoek (nog) niet tot minder bloedingen of trombose.

Het verpakken van VKA's via medicatie op rol was echter niet voor alle patiënten even effectief. Daarom zijn subgroep analyses uitgevoerd om specifieke groepen patiënten te identificeren die het meest baat hadden bij de toepassing van medicatie op rol **(Hoofdstuk 8)**. De interventie was effectiever bij patiënten met een ordeningsprobleem (11.6% TTR toename) in vergelijking met patiënten zonder ordeningsprobleem (2.6% TTR afname). Het effect van de interventie leidde tot een hogere, echter niet significante, TTR toename bij kwetsbare patiënten (8.2%) in vergelijking met niet kwetsbare patiënten (0.5%), bij patiënten van 80 jaar of ouder (8.1%) in vergelijking met patiënten tussen 65 en 79 jaar (3.8%) en bij patiënten met een lage zelf gerapporteerde therapietrouw (10.6%) in vergelijking met therapietrouwe patiënten (3.1%). Het geslacht van de patiënt, het cognitief functioneren, het aantal medicijnen in gebruik of de opvattingen van patiënten over de behandeling met VKA's hadden geen invloed op het effect van de interventie. Onze conclusie is dat de kwaliteit van de antistolling therapie verbeterd kan worden door VKA's via medicatie op rol te verstrekken. Patiënten met ordeningsproblemen profiteerden het meest. De interventie lijkt tevens effectief voor kwetsbare patiënten en patiënten ouder dan 80 jaar.

Afsluitend bediscussiëren we in **Hoofdstuk 9** de implicaties van de verschillende onderzoeken in een bredere context door drie vragen te bespreken. 1) Welke patiënten komen in aanmerking voor het gebruik van medicatie op rol? 2) Hoe kan de farmaceutische patiëntenzorg rondom patiënten met medicatie op rol worden geoptimaliseerd? 3) Hoe kan in de toekomst het effect van medicatie op rol verder worden onderzocht?

We hebben aangetoond dat medicatie op rol voornamelijk wordt gestart voor patiënten met een ordeningsprobleem. Om ordeningsproblemen tijdig te signaleren wordt geadviseerd patiënten ouder dan 80 jaar of kwetsbare patiënten periodiek te screenen op mogelijke ordeningsproblemen. Om dit waar te kunnen maken, moeten openbare apothekers een meer proactieve houding aannemen en duidelijke afspraken maken met voorschrijvers en thuiszorgmedewerkers om deze hoog risicopatiënten

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te identificeren en screenen. De ontwikkelde vragenlijst kan toegepast worden om patiënten te screenen op mogelijke ordeningsproblemen waarbij de korte versie van de vragenlijst het meest geschikt lijkt voor toepassing in de praktijk. De vragenlijst is echter niet als checklist bedoeld, het dient als ondersteunend hulpmiddel. Sommige patiënten kunnen ondanks veel problemen toch nog uit de voeten met reguliere verpakkingen, terwijl bij andere patiënten een klein aantal problemen al onoverkomelijk kan zijn. Uiteindelijk moet het initiëren van medicatie op rol gebaseerd zijn op een gezamenlijke besluitvorming tussen de patiënt en de zorgverlener.

Over het algemeen hebben gebruikers van medicatie op rol veel medicatie, zijn ze oud, kwetsbaar of hebben (beginnende) cognitieve problemen. Deze patiënten hebben daarom een hoog risico op medicatie-gerelateerde ziekenhuisopnames. Om dit te voorkomen moeten openbare apothekers zich nog meer richten op de farmaceutische patiëntenzorg voor deze gebruikers. Zo hebben apothekers bijvoorbeeld een grotere verantwoordelijkheid om veranderingen in het geneesmiddelregime door te voeren in de medicatie op rol van de patiënt. Om het aantal acuut doorgevoerde wijzigingen in de farmacotherapie te beperken, wordt aanbevolen om in eerste instantie onderscheid te maken tussen symptomatische (acute aanpassing) en preventieve behandeling (uitgestelde aanpassing). In de loop van de tijd is de verwachting dat de gezondheidstoestand van de patiënt langzaam verslechtert. Als gevolg van de achteruitgang van de gezondheidstoestand van de patiënt moeten apothekers(assistenten) het gebruik van medicatie op rol periodiek evalueren met patiënten. Het verdient de aanbeveling het gebruik persoonlijk face-to-face te evalueren. Echter dient niet alleen het gebruik van het systeem geëvalueerd worden, ook de kwaliteit van de farmacotherapie moet worden geëvalueerd door een apotheker waarbij extra aandacht wordt besteed aan de mogelijkheid medicatie af te bouwen of geheel te staken ('deprescribing'). Om apothekers te stimuleren meer farmaceutische patiëntenzorg voor medicatie op rol gebruikers te verlenen, dient de financieringsstructuur van openbare apotheken aangepast te worden. Er dient meer nadruk op een vergoeding voor de geleverde zorg te komen in plaats van enkel voor logistiek. Daarnaast is er een dringende behoefte aan een grondige herziening van de medicatiebewaking om de medicatieveiligheid van medicatie op rol gebruikers effectief en doelmatig uit te kunnen voeren.

Ondanks het wijdverbreide gebruik van medicatie op rol, is er beperkt wetenschappelijk bewijs voor de effectiviteit van deze systemen. Wij hebben laten zien dat met het toepassen van medicatie op rol de TTR van de patiënt positief kan worden beïnvloed. Om ook het effect van medicatie op rol op andere gezondheidsuitkomsten te evalueren is meer onderzoek nodig. Dit kan zowel worden onderzocht middels RCT's

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als databasestudies. Echter is het vinden van een uitkomst die objectief het effect van medicatie op rol weergeeft een uitdaging. Uiteindelijk is een formele kosteneffectiviteit analyse noodzakelijk waarbij alle kosten en baten voor zowel de nulde-, eerste- als tweedelijnsgezondheidszorg dienen te worden meegenomen.

Concluderend zijn in dit proefschrift een reeks van onderzoeken beschreven waarin de effecten van medicatie op rol vanuit verschillende perspectieven zijn belicht. De bevindingen in dit proefschrift bevestigen de aanname dat medicatie op rol ondersteunend is in het medicatiebeheer en gebruik van de patiënt, met name voor patiënten met een ordeningsprobleem. Om de uitdaging van de vergrijzende bevolking en de verwachte toename van het gebruik van medicatie op rol het hoofd te bieden, is actie op verschillende niveaus nodig. Het verdient aanbeveling dat beleidsmakers en zorgverzekeraars veranderingen doorvoeren in de financiering van de farmaceutische patiëntenzorg zodanig dat apothekers worden gestimuleerd en beloond om meer farmaceutische patiëntenzorg te bieden voor deze specifieke groep patiënten. Echter nog belangrijker is dat openbaar apothekers zelf meer initiatief nemen en zich profileren als zorgverlener. Daarbij past het om actief de samenwerking met andere zorgverleners te zoeken om de farmaceutische zorg voor deze specifieke groep patiënten te verbeteren.

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Dankwoord

Het zit erop. Met het schrijven van dit dankwoord sluit ik een periode van 5 jaar af waarin ik veel heb geleerd maar dat ging niet zonder slag of stoot. Ik ben dit avontuur aangegaan om mezelf verder te ontwikkelen. Vanaf jongs af aan mag (of moet, het is maar net hoe je het bekijkt) naar school. Van de basisschool tot en met een opleiding aan de universiteit word je als mens uitgedaagd tot verdieping en ontwikkeling. Dit ging mij over het algemeen goed af en, buiten een periode op de middelbare school nagelaten, ben ik voor mijn gevoel nooit echt 100% uitgedaagd. Wel vond ik het altijd leuk om te leren, te ontwikkelen en uit mijn comfort zone te treden. Na het behalen van mijn master vroeg ik mij af wat de volgende stap in mijn ontwikkeling zou zijn. Ik was in de gelukkige omstandigheid om werkzaam te zijn in de Stevenshof waar tal van collega's zijn gepromoveerd. Al snel kwam de kans om ook deze uitdaging aan te gaan. Terugkijkend op de afgelopen 5 jaar kan ik wel stellen dat ik niet eerder voor zo'n grote uitdaging heb gestaan. Gekscherend heb ik het meermaals vergeleken met hoogspringen, niet dat ik deze sport overigens beoefen. Hoogspringen is in mijn ogen springen over een lat welke zo hoog ligt dat dit onhaalbaar lijkt. Opgeven is echter geen optie. Er moest dus getraind worden. Niet met 85 of 99% inzet maar met volledige toewijding. Dat ben ik dan ook gaan doen, piekerend over de juiste aanloop, afzet, timing, techniek. Allemaal met als doel om verder te ontwikkelen. Ik ben dan opgelucht en blij dat het me is gelukt, ik ben over die lat. Maar makkelijk was het niet.

Marcel, allereerst wil ik jou bedanken. Jij was mijn eerste promotor waar ik mij heel gelukkig mee prijs. Gedurende al die jaren heb ik me verbaasd hoe jij ondanks een drukke agenda altijd tijd weet te maken voor begeleiding. Je was altijd op de hoogte van alle ontwikkelingen binnen het promotietraject en kwam met verfrissende suggesties wanneer ik niet meer wist hoe we verder moesten gaan. De samenwerking was niet enkel professioneel want snel bleek dat wij veel dezelfde interesses delen. Dat heeft voor mij de begeleiding extra speciaal gemaakt. Enkele voorbeelden zal ik dan ook niet snel vergeten zoals de masterclass in Heidelberg met een hotel naast de Kulturbrauerei met diverse soorten Naturtrüb, de Utrechtse estafette marathon, en als afsluiter uiteraard het gezamenlijke SIR diner. Ik ben dan ook blij dat onze samenwerking zal voortduren binnen de academisering van apotheek Vleuten. Marcel heel erg bedankt!

Rob, jij sloot aan als 2e promotor in het begin van 2016. Zoals je zelf eens mooi verwoordde bemoei je je graag met de inhoudelijke invulling van het vak van apothekers. Je bent dan ook tot je eigen verbazing opvallend veel onder de apothekers te vinden. Maar dat is niet voor niets want als geriater bleek jij een uitstekende aanvulling te zijn op een team van drie eigenwijze apothekers. Veelal zorgde een simpele vraag ervoor

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dat antwoorden scherper geformuleerd en meer toepasbaar voor de praktijk werden. Door de samenwerking en verschillende gezichtsvelden is het proefschrift uiteindelijk geworden zoals het nu hier voor ons ligt. Ik wil je heel erg bedanken voor je inbreng, toewijding, opmerkingen en flexibiliteit. Ik kan me niet anders voorstellen dat we elkaar vaker gaan treffen op diverse plekken en daar verheug ik me op.

Henk-Frans, mijn reis startte bij jouw finish. Ik ben verder gegaan op de vele vragen die jouw promotieonderzoek naar voren bracht. Uiteraard sloot jij aan in de rol van copromotor. Ik heb de invulling die jij hieraan gaf als zeer waardevol ervaren. Duidelijk was dat jij deze reis al had afgelegd. Waar nodig kun je schakelen tussen de grote lijnen en de details. Als het moet ben je meegaand en soms heb je een duidelijke eigen mening. Je kon daarbij volhardend zijn maar nooit eigenwijs, de uiteindelijke keuze was aan mij. Naast de rol van promovendus en copromotor waren we binnen de apotheek ook nauwe collega's. Ik waardeer de oprechtheid in onze samenwerking waarin alles besproken en benoemd kan worden. Soms zijn we het oneens met elkaar en de enkele keer dat we er niet uitkomen accepteren we dat we er niet uitkomen. Vanaf nu begint een nieuw hoofdstuk met Apotheek Vleuten. Ik ben trots dat ik deze kans krijg en heb heel veel zin om de komende jaren de academisering samen verder vorm te geven. Hierbij wil ik voorstellen om zo nu en dan de gezamenlijke overleggen te blijven laten plaatsvinden onder genot van een speciaalbiertje. In het verleden is dat meer dan goed bevallen.

Alle leden van de leescommissie, Toine Egberts, Ton de Boer, Roger Damoiseaux, Kees Kramers en Suzanne Cannegieter, ik wil jullie bedanken voor het lezen en goedkeuren van mijn proefschrift. De commissie is mijn inziens een mooie afspiegeling van de verschillende beroepsgroepen die raken aan de verschillende onderwerpen in dit proefschrift.

We hebben getracht de toepassing van medicatie op rol via verschillende perspectieven en onderzoeksmethoden te benaderen. Hiervoor hebben we gebruik gemaakt van verschillende onderzoeksmethoden. Een aantal personen hebben hier een cruciale rol in gespeeld en wil ik daarom expliciet bedanken. Allereerst Felix, al in 2014 hebben wij gesproken over de uiteindelijke uitgevoerde studie naar het effect van medicatie op rol onder gebruikers van vitamine K-antagonisten. De uiteindelijke uitwerking is een mooie samenwerking geworden tussen de trombosedienst Leiden en de apothekers. Zonder jouw input en inbreng was dit niet mogelijk geweest. Na de uitvoering moesten alle gegevens geanalyseerd worden. Voor je hulp en geduld wil ik je heel erg bedanken Svetlana. Ondanks mijn vele telefoontjes en mailtjes bleef je altijd behulpzaam en geduldig. Dank daarvoor! Als laatste wil ik graag Marloes bedanken voor je hulp bij de

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analyse van de PHARMO database. Ik had het 'geluk' te moeten werken met SAS wat een absolute uitdaging te noemen is. Zonder jouw hulp was dit nooit en te nimmer gelukt. Jij verdient daarvoor een hele grote stikker!

Binnen de verschillende onderzoeken hebben we niet vaak voor de gemakkelijke weg gekozen. Het doel van het proefschrift was om invulling te geven aan de dagelijkse praktijk. Het gevolg hiervan is dat de verschillende onderzoeken ook daadwerkelijk uitgevoerd zijn in de praktijk. Ik wil dan ook alle deelnemende apothekers, farmaceutisch consulenten, en apothekersassistenten bedanken voor hun bijdrage. Zonder jullie hulp van was dit nooit gelukt. Dank voor jullie inzet!

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promoveren en bood de ruimte om beide banen te combineren. Jij hebt een duidelijke visie en weet mensen op een mooie manier te inspireren en motiveren. Uiteindelijk heeft Annemieke jouw rol als directeur van de SIR overgenomen. Ook jou wil ik graag bedanken voor de begeleiding en mogelijkheden om dit traject succesvol af te ronden. Het is een voorrecht om bij de SIR te mogen werken. Ik heb de SIR altijd als een warme organisatie ervaren waarin iedereen bevlogen is om de patiëntenzorg verder te helpen. Naast deze bevlogenheid is er ook ruimte voor plezier en een goed gesprek. Juist deze mix maakt het werken bij de SIR zo prettig. Ik wil graag toch nog 1 collega er speciaal uitlichten want zoals jij het omschreef kan ik het niet overtreffen. Sanne, wij waren collega-ApIOS-openbaar-apotheker-onderzoeker-externe-promovendus-buddies. Doordat we dezelfde startdatum hadden, begaven we ons vaak op hetzelfde punt. De unieke combinatie van werkzaamheden met (bijna) hetzelfde promotieteam zorgde voor vele overeenkomstige hobbels. Juist dan was het erg fijn om even te kunnen sparren, spuien en soms irritaties te kunnen delen. Maar ook daarnaast was het gewoon heel gezellig tijdens de verschillende congressen, symposia en cursussen. Juist de klik op vriendschappelijk gebied zal ik koesteren.

Zoals mogelijk bekend heb ik mijn promotietraject gecombineerd met baan als openbaar apotheker bij Academische Apotheek Stevenshof. In 2012 kwam ik als jochie binnen. Nu, bijna 7 jaar later, vertrek ik met pijn in mijn hart. Ik kan oprecht zeggen dat ik altijd met veel plezier naar mijn werk ga en dat is erg prettig. Dat komt voornamelijk door de collega's met wie we dagelijks samenwerken. Ook hier wordt hard werken gecombineerd met veel plezier. Ik wens jullie een rustige tijd toe, al zullen jullie me nog steeds af en toe stampend en zwaaiend met mijn sleutels de trap af horen komen.

In mijn dankwoord wil ik toch even alle apothekers bedanken met wie ik bij Apotheek Stevenshof heb samengewerkt. Door de combinatie van verschillende functies en mijn soms iets mindere planningscapaciteiten heb ik meermalen een beroep op jullie moeten doen met ruilverzoekjes. Gelukkig was er altijd een oplossing. Henk-Frans, Leonie, Anne-Margreeth, Adrianne, Firdaouss, Marcel en Hanneke dank hiervoor. Ook Gert moet ik bedanken. Jij had de pech de ApIOS te zijn in het laatste deel van mijn promotie. Dat betekende nog veel meer ruilverzoekjes voor jou die altijd zijn gelukt. Ondanks dat je golft, ben je een topgozer.

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het veelal tijd voor feest, sportieve activiteiten, spelletjes, plezier en goede gesprekken. De herinneringen zijn talrijk, van (fiets)vakanties, Bij.BRT. diners, Sinterkerst, proeverijen van Vriendenbrouwerij de Baarsjes, buitenspelen op festivals tot aan vele late avonden in de Figurantenbar. Maar het leven is niet altijd één groot feest, soms is het minder leuk en verdrietig. Ook daar is ruimte voor. Ik prijs mij gelukkig met jullie als vrienden en kijk uit naar nieuwe avonturen. Laten we het leven samen blijven vieren!

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List of publications

International publications presented in this thesis

- Mertens BJ, Kwint HF, van Marum RJ, Bouvy ML. Are multidose drug dispensing systems initiated for the appropriate patients? *Eur J Clin Pharmacol*. 2018;74:1159-64.
- Mertens BJ, Kwint HF, van Marum RJ, Bouvy ML.Patients' experiences with multidose drug dispensing: a cross sectional study. *Int J Clin Pharm*. 2019;41:104-12
- Mertens BJ, Kwint HF, van Marum RJ, Bouvy ML. Immediate or deferred adjustment of drug regimens in multidose drug dispensing systems. *Res Social Adm Pharm*. 2019;15:303-09

Other publications related to this thesis

- Kwint HF, Mertens BJ, Mulder-Wildermors LGM. Minder geneesmiddelkennis bij medicatierolgebruikers. *Pharm Weekbl*. 2014;149-39.
- Mertens BJ, Kwint HF, Bouvy ML, van Marum RJ. Medicatie op rol, wat komt er bij kijken. *Ned Tijdschr Geneeskd*. 2017;161:D1770
- Mertens BJ, Kwint HF, van Marum RJ, Bouvy ML. Acute wijziging medicatierol is tijdrovend en risicovol. *Pharm Weekbl*. 2017;152–13

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About the author

Bram Joeri Mertens was born 17 January 1986 in Nieuw-Ginneken, the Netherlands. He lives in Amsterdam together with his girlfriend and two children. He obtained his pharmacy degree at the Utrecht University in 2012. During his study, he was a trainee at Apotheek Farmadam and Academische Apotheek Stevenshof. Within these internships his interest about multidose drug dispensing and academic research was awakened which is combined in the work presented in this thesis.

After he obtained his Master of Science degree in Pharmacy, he started working at the Academische Apotheek Stevenshof as a community pharmacist in 2012 which he combined with a post-academic advanced community pharmacist education program which he completed in 2015. Since 2014, he combined his work as community pharmacist and training program with a research position at the SIR Institute for Pharmacy Practice and Policy where he started with his PhD research with the main objective: multidose drug dispensing, for older patients in primary care. Therefore, he was affiliated to the Division of Pharmacoepidemiology and clinical pharmacology of the Utrecht Institute for Pharmaceutical Sciences of the Utrecht University.

Since 2014, he is a member of the Special Interest Group "Cardiovascular diseases" of the Royal Dutch Pharmacists Association (KNMP). In 2014 he became a member of the commission "Interacting medication vitamin-K antagonists" from the Royal Dutch Pharmacists Association (KNMP), Federation of Dutch Anticoagulation clinics and the Health Base Foundation.

After completing this PhD, he will start working as a managing community pharmacist at Apotheek Vleuten. He will continue to combine this new position with his work at the SIR Institute for Pharmacy Practice and Policy with special interest for pharmacy practice research.

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