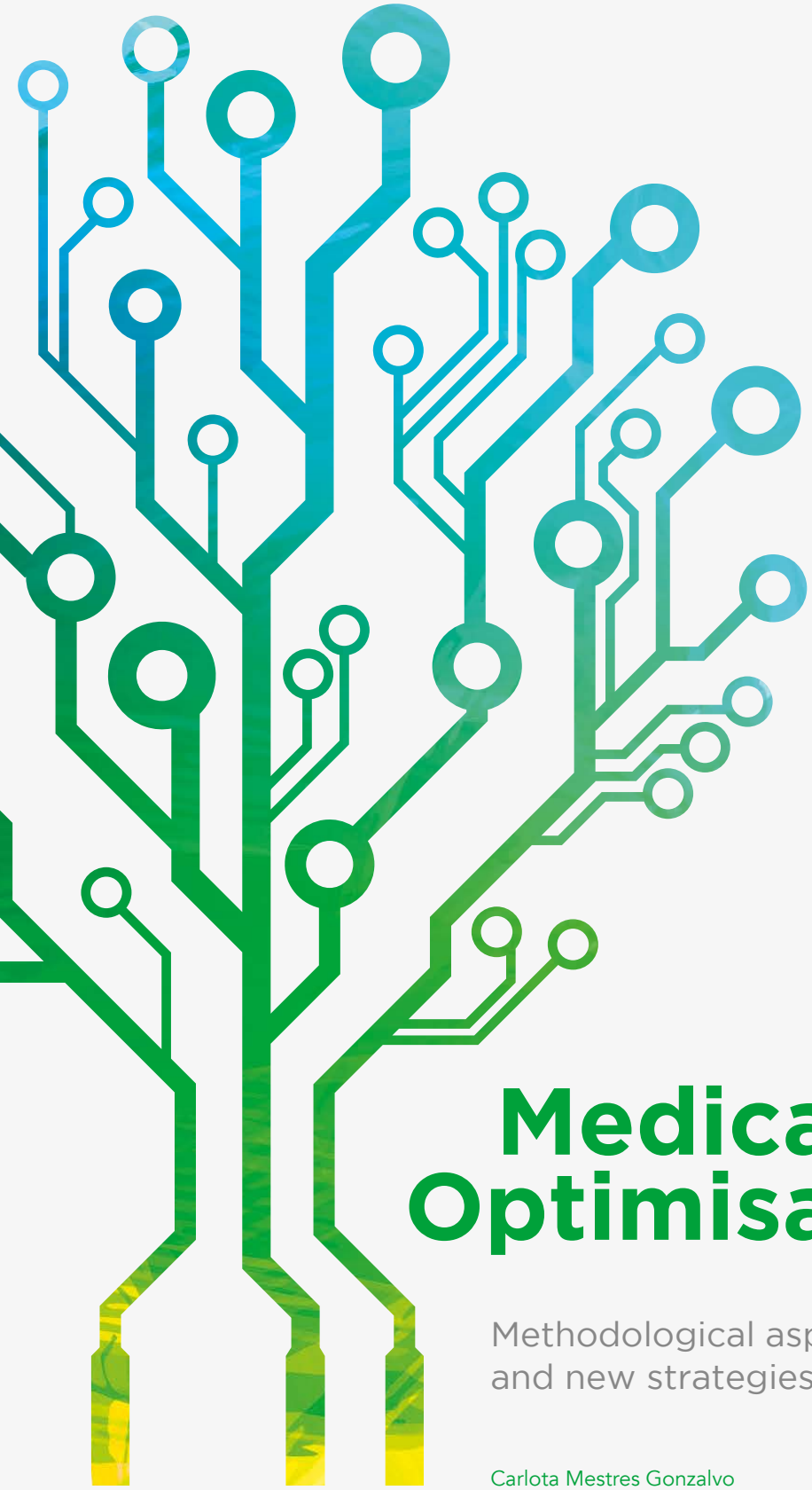
Medication optimisation



Medication Optimisation

Methodological aspects and new strategies

Carlota Mestres Gonzalvo

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MEDICATION OPTIMISATION

Methodological aspects and new strategies

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Chapter 1

General introduction

Introduction

Polypharmacy and medication review

Polypharmacy can generally be defined as the use of more than a certain number of drugs, regardless of their appropriateness [1–3]. In the Netherlands, polypharmacy has more specifically been defined as the chronic use of five or more drugs from different therapeutic groups or subgroups [4].

In the nursing home population, polypharmacy is highly prevalent: it is estimated that one out of every three patients is polymedicated [5], and given their considerable frailty, these patients are extra prone to adverse drug reactions (ADRs). In addition, management of comorbidities and/or complex organ function impairment is often challenging [6-11]. Furthermore, polymedicated patients are also at risk of suffering from inappropriate prescribing in the form of underprescription, as it has been demonstrated that underprescription increases significantly with the number of medicines used [12]. Prescribing new drugs that are necessary might imply new ADRs, more interactions and/or poor adherence [12].

In the nursing home population, a prevalence as high as 40% is found for receiving potentially inappropriate medication. Therefore, several initiatives have been taken to reduce inappropriate medication. The definition of inappropriate medication was first established in the “Beers” criteria [13, 14] for the nursing home population. This list contains different guidelines to help healthcare professionals improve the safety of prescribed medications for older adults. The “Beers” list mostly emphasises medications that are unnecessary, which helps reduce polypharmacy, drug interactions, and ADRs. The “Beers” criteria were created by a geriatrician through a consensus panel of experts using the Delphi method. The criteria were originally published in the Archives of Internal Medicine in 1991 and were last updated in 2015 [15]. The STOPP/START criteria (Screening Tool of Older Person's Prescriptions and Screening Tool to Alert doctors to Right Treatment) were first developed in 2008 following the Delphi method as well and were last updated in 2015 [16, 17]. The STOPP/START criteria established not only inappropriate medication but also missing medication, covering inappropriate prescribing in the form of underprescription [16]. As a result of inappropriate prescribing, drug-related problems (DRPs) can occur; DRPs are defined as “an event or a circumstance involving drug therapy that actually or potentially interferes with health care outcome” [18]. In the recent HARM study, it was established that 5.6% of the unplanned hospital admissions in the Netherlands were medication related, and it has been suggested that half of these hospital admissions could have been prevented had different criteria

been applied in a timely manner. These results strengthen the need for routine medication reviews and treatment optimisation [19, 20, 21].

The latest definition of a medication review by the PCNE (Pharmaceutical Care Network Europe) is a structured evaluation of a patient's medicines, with the aim of optimising medicines use and improving health outcomes [2]. This entails detecting DRPs and recommending interventions and thus aiming at preventing unplanned hospital admissions related to medication [2].

In the Netherlands, the Dutch Healthcare Inspectorate (IGZ: Inspectie voor de Gezondheidszorg) requires that at least one medication review is performed yearly by a physician together with a pharmacist for all residents of nursing homes; this is an important and sensible measure to assure the quality of prescribing regimes. However, following this requirement implies a substantial extra workload for the healthcare professionals involved. In addition, in this medication review, the information given by the nursing staff and the patient him/herself should also be taken into account [22].

The feasibility of systematic medication reviews is debated. Medication reviews are a time-consuming process, and in daily practice, this unfortunate situation leads to a non-continuous medication review process, implying major consequences that may range from an increased number of potential ADRs and/or DRPs, unnecessary hospitalisations and, at worst, death. Furthermore, a Cochrane review on interventions to improve the appropriate use of polypharmacy for older people concluded that even though such interventions appear beneficial in terms of reducing inappropriate prescribing and medication-related problems, it remains unclear whether interventions to improve appropriate polypharmacy result in clinically significant improvements [23]. Subsequently, a recent systematic review and meta-analysis from Huiskes et al. on the quality of medication reviews concludes that traditional medication reviews have no effect on quality of life and minimal effect on clinical outcomes (no effect on mortality, hospital admissions/healthcare use, physical and cognitive functioning, and a minimal effect on the number of patients falling) [24]. They suggest an end to performing cross-sectional medication reviews as standard care. The major pitfall in this conclusion is that medication reviews are performed as a cross-sectional intervention at an arbitrary moment during a patient's drug therapy. Therefore, it has been suggested that longitudinal or continuous medication therapy management, targeting specific risk moments, could be a better alternative [24].

Computerised Clinical Decision Support Systems (CCDSS) and Clinical Rules (CR)

Developing and assessing new care interventions are keys to optimising pharmacotherapy and thus limiting the negative effects of polypharmacy [21]. Studies have suggested that the elements of a successful medication review include use of a standardised method performed by pharmacists and physicians as well as use of laboratory data and a complete medical and drug history [1, 20, 25-28].

A CCDSS can be defined as a decision-aiding tool that provides health care professionals with clinical knowledge and patient-related information, intelligently filtered or presented at appropriate times, to enhance patient care [29-31]. The development of CCDSSs has become an ongoing process of sophisticated generating systems that link patient characteristics with computerised knowledge bases, using algorithms (CRs) and generating patient-specific assessments or treatment recommendations [32-38]. CCDSSs and CRs are conceived to support a range of clinical daily tasks by integrating the electronic medical record systems and the computerised physician order entry systems (CPOEs) in such a way that reminders or warnings can be sent to guide both drug and dosage selection processes and identify deviating laboratory test results, adverse drug reactions, allergies, possible interactions and duplicates [39-43]. Furthermore, CCDSSs and CRs can target a wide range of actions within the prescribing process, such as treatment monitoring, dose adjustments, and stopping or dwindling therapy, and they can generate lists of patients eligible for a particular intervention by following guidelines or specific protocols [31, 44-51].

Objective and outline of this thesis

The primary objective of this thesis is to explore the current situation of medication optimisation during the medication review process and evaluate possible improvements and new strategies.

This primary objective leads to several research questions:

Which steps are essential for a transition from a standard medication review process to medication optimisation by means of a CCDSS?

The first step in the transition towards a longitudinal medication therapy management is described in **Chapter 2**, where the development of a CCDSS is presented that, independent of the prescribing software, continuously monitors all prescribed

drugs while taking into account co-medication, laboratory-data and co-morbidities.

Which information is crucial to perform a high-quality medication review and how do healthcare professionals use such information?

Medication reviews are considered important in maintaining a high quality of pharmacotherapy. However, there is a large variation in the quality of these reviews. In **Chapter 3**, an explorative survey of variables that may lead to a high-quality medication review is described. These variables (drug indications, medical history, and laboratory values) are used in **Chapter 4** to evaluate to what extent they are used when performing medication reviews for nursing home patients.

How does the BZ/Z (benzodiazepine and benzodiazepine-related drugs) CR perform in daily practice?

A clinical rule aimed at benzodiazepine use optimisation was developed. This CR alerts whenever a benzodiazepine or benzodiazepine-related drug is chronically used. In **Chapter 5**, the performance of this CR and the feasibility of successfully stopping a chronically used benzodiazepine or benzodiazepine-related drug in the nursing home population is explored.

Is it possible to predict delirium in a hospitalised patient with a CR?

A delirium or acute confused state is a transient attention and cognition disorder that develops over a short period of time and occurs mainly in hospitalised patients and people aged 60 years and over. Delirium is an under-diagnosed, severe, costly and often preventable disorder. A fully automated CR to predict delirium (DEMO) in older people was developed, and in **Chapter 6**, the predictive value of the DEMO was validated in the clinical setting.

How should a clinical trial for CCDSS be designed?

Due to the lack of evidence concerning the benefits of medication reviews performed in the nursing home setting, we propose a study aiming to demonstrate a positive effect that a CCDSS, as a health care intervention, may have on the target population. In **Chapter 7**, the design of the study in which a CCDSS is actually used to support medication reviews in the nursing home population is presented.

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Chapter 2

Development of a computer system to support medication reviews in nursing homes

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Development of a computer system to support medication reviews in nursing homes. International journal of clinical pharmacy. 2013 Oct 1;35(5):668-72.

Abstract

The frail elderly populations of nursing homes frequently use drugs and suffer from considerable comorbidities. Medication reviews are intended to support evidence-based prescribing and optimise therapy. However, literature is still ambiguous regarding the optimal method and the effects of medication reviews. Innovative computerised systems may support the medication reviews in the future. We are developing a clinical decision support system (CDSS) that, independently of the prescribing software, continuously monitors all prescribed drugs while taking into account co-medication, laboratory-data and co-morbidities. The CDSS will be developed in five phases: (1) development of the computerised system, (2) development of the clinical rules, (3) validation of the CDSS, (4) randomised controlled trial, and (5) feasibility for implementation in different nursing homes. The clinical decision support system aims at supporting the traditional medication review.

Introduction

In 2009 11.8 million of the Dutch population (71.6%) used prescription medication. A considerable number, 2.3 million (14.3%), using prescribed medication were 65 years of age or older.

In 2009, nursing homes and homes for the elderly provided care to approximately 155.000 patients daily [1]. The population of nursing homes are often frail given their inability to withstand negative events. Frail elderly is defined as the combination of biological, functional, cognitive, and clinical aspects of the elderly [2].

Polypharmacy, the use of many different drug combinations, increases the risk of adverse effects, often causes problems with patient compliance, increases the likelihood of inappropriate prescription, and simultaneously may cause suboptimal treatment because the probability of underprescription paradoxically increases with the number of drugs used [3, 4]. A prevalence of 12% and 40% was found for potentially inappropriate medication in community-dwelling elderly and nursing home residents respectively [5]. Polypharmacy also has other consequences such as increased drug interactions, adverse drug reactions, and non-adherence. Decreased physical functioning and ability to carry out instrumental activities of daily living, poorer nutritional status, increased risk of geriatric syndromes, and more falls are also associated with polypharmacy [6].

Evidence-based guidelines for geriatrics and nursing homes are limited since older patients and patients with comorbidities are generally excluded from clinical trials [7].

Medication prescription should be based on the physical condition of the patient with special interest in the hepatic and renal function. Regular revision of the medication should be considered, especially in elderly patients.

Medication reviews

A medication review is defined as a structured evaluation of the patient's medicines, aimed at reaching agreement with the patient, optimising the impact of medicines and minimising the number of medication-related problems while considering medical history and laboratory values [8]. The Dutch Healthcare Inspectorate expects all residents of nursing homes (twice a year) and homes for the elderly (once a year) to receive a medication review by a physician and a pharmacist. In this medication review the information given by the nursing staff and the patient him/herself should be taken into account [9].

Several methods have been described to optimise prescribing and to support medication reviews [10, 11]. Alldred et al. showed in a review for optimising prescribing in older people in care homes that there is no evidence for an effect on primary outcomes such as adverse drug events, hospital admission, and mortality. The interventions did lead to the improvement of medication-related problems [12]. This shows that the mainly pharmacist-initiated medication reviews create a multidisciplinary interaction between physicians, nurses, and pharmacist which optimises prescriptions and therapy.

It seems reasonable to assume that manual methods used to support medication reviews are as good as the professional using it. Outcomes will depend on variables such as knowledge of guidelines or perhaps the focus of the healthcare professionals. A study by Thier et al. has shown that the adherence to guidelines in clinical practice is low for many chronic diseases [13]. Also, the current methods to support medication reviewing are time-consuming and have temporary effects since they are used manually and not continuously.

Therefore, a computerised system might support a continuous, complete and reproducible medication review.

Clinical rules are able to combine the pharmacy, clinical as well as laboratory data according to specifically developed algorithms (see figure I). A computer system that can execute the algorithm based clinical rules is also referred to as a Clinical Decision Support System (CDSS) and it can provide around the clock surveillance. Studies have shown that guidelines and clinical management tables integrated in a CDSS help healthcare professionals to avoid errors and improve clinical practice [14].

Moreover, the benefits of using a CDSS in a hospital setting are also shown [14, 15]. Nevertheless, the use in nursing homes is still limited [16]. Alldred et al. also concluded that cluster-randomised controlled trials testing a CDSS are needed to determine important population related-outcomes [12].

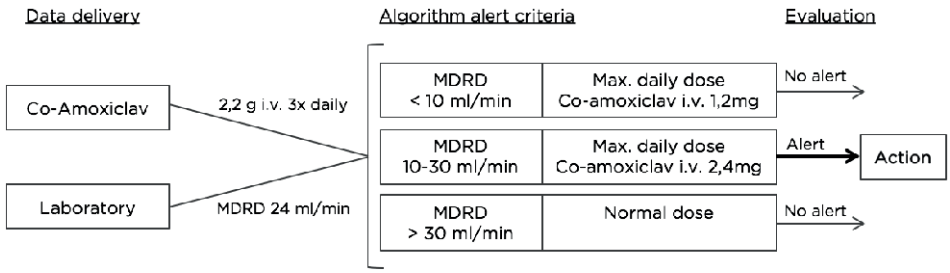

Figure I. An example of an algorithm based clinical rule combining laboratory and pharmacy data

New Approach

The use of a CDSS seems to be the best direction for further optimisation and improvement of drug therapy. Currently the alerts of clinical rules used in a CDSS are strongly related to suggestions made in a medication reviews, however the alerts are underdeveloped and not yet validated for the nursing home population. It is our aim to develop a CDSS to support the traditional medication review in nursing home patients which monitors continuously the drugs used by the patient, taking into account co-medication, laboratory-data and other clinical relevant data. This CDSS should be validated, easy to implement, EPS independent, easy to use in daily practice, and provide information on previous alerts and undertaken actions. Furthermore, the accessibility of different electronic patient's records (EPR) is pivotal for the usage of clinical rules with the primary indication for a drug as a starting point of the algorithms.

Study Phases

To achieve this, we have planned to execute the SCREEN study -Supporting Clinical Rules in the Evaluation of Elderly patients with Neuropsychiatric disorders. This study is divided in five phases (figure II) and will be discussed below.

1. *Development of a computerised system:* The first phase is the development of a CDSS, which can use extractions from different electronic prescribing systems (EPS) and electronic patient's records (EPR). When the CDSS can use different EPS's, it can be implemented in different nursing homes and probably other clinical settings such as primary care, homes for the elderly and hospital care.

2. *Development of the clinical rules:* Clinical rules are the content of the CDSS. The clinical rules will be divided into different topics; 1) clinical rules for general medicine, 2) laboratory values, and 3) neuropsychiatric disorders and indications. Each topic will be systematically approached through an exploration of the literature, guidelines and summaries of product characteristics. A hospital pharmacist and a physician geriatrician will explore the available literature first and design clinical rules. The concept clinical rules will then be reviewed by an expert panel consisting of hospital pharmacists, geriatricians, nursing home physicians, and physicians in neuropsychiatry and old age psychiatry.

   The clinical rules for general medicine and laboratory values will consider dose adjustment for impaired renal and/or hepatic function, drugs contra-indicated for specific diseases and necessary laboratory checks to optimise

pharmacotherapy such as the prescribing of an ACE-inhibitor in impaired renal failure and monitoring the potassium levels. The development of clinical rules based on guidelines will depend on the extraction of the EPR-data. For instance, a clinical rule specifying the optimal therapy after a myocardial infarction will be dependent of the known indication from the EPR-extraction.

3. *Validation of the CDSS:* A high efficiency of the alerts in the CDSS is of great importance because many false positive alerts will lead to alert fatigue. Other studies involving prescribing software have shown the relation between the non-adherence of prescribing physicians and the appearance of too many non-relevant warnings [17, 18]. To ensure a high efficiency the CDSS with the clinical rules will be validated via three methods. First the CDSS will be validated technically to ensure a correct link between the CDSS and the used clinical information. This technical validation will be done by creating a fictive patient group which will include patients with every possible parameter variation in the clinical rules. By doing this, false negative alerts will be prevented. Secondly, when possible the clinical rules will be validated retrospectively by using a patient database.

   Thirdly, a prospective validation will be performed to measure the effect of the clinical rule in daily practice. Whether a certain clinical rule is effective or not, can also be measured by evaluating the responses of the physicians. Alerts from clinical rules with no actions by the physicians should be evaluated on clinical relevance or specificity. The prospective validation will further facilitate the efficiency of the clinical rules.

4. *Randomised controlled trial:* A randomised controlled trial in nursing homes will be performed to show the possible benefits of the medication review performed by the CDSS in comparison with the traditional medication review. Outcomes are the total number of interventions suggested by the programme versus a medication review, quality of life-score, reported adverse effects (such as falling and delirium), and number of drug-related hospital admissions.

5. *Feasibility:* The final phase is to implement the system in other nursing homes with different software systems. The researchers will supervise this phase. The implementation in new nursing homes will need to overcome problems which might vary from technical problems extracting data from different EPS' and ERP's to the introduction of a new system in an organisation.

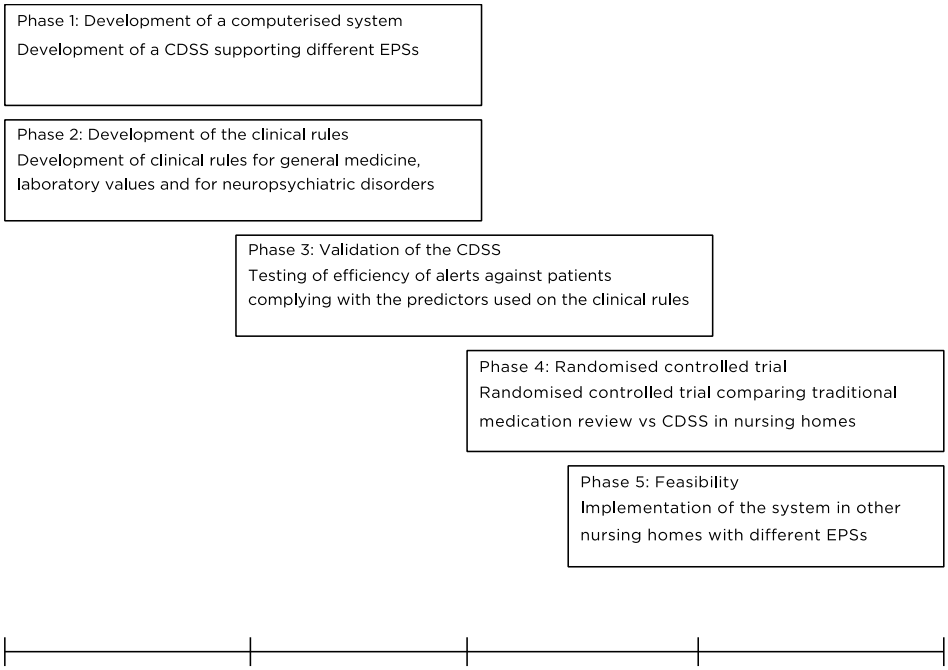

Figure II. A schematic overview of the five phases. The timeline shoes the start of each phase in relation to the other phases.

Conclusion

The SCREEN-study aims to develop a generic applicable CDSS for nursing homes able to support medication reviews. The clinical trial will show the feasibility of the system to perform medication reviews in nursing homes. The lack of patient input is a limitation of the system should it replace the traditional medication review. However, the CDSS is expected to support the traditional medication review and it can serve as a second-generation medication surveillance system. In our opinion the development of a system, which is able to reduce the time-consuming process of a traditional medication review and create high-quality suggestions for therapy optimisation, will be unique.

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Chapter 3

Covariates that influence the quality of a medication review

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Covariates that influence the quality of a medication review. European Journal of Hospital Pharmacy: Science and Practice 21.1 (2014): 18-21.

Abstract

Background: Medication reviews are considered to be important to maintain a high quality of pharmacotherapy. There is a large variation in the quality of these reviews.

Aim: To evaluate the covariates that may lead to high quality medication reviews and to establish their relative importance.

Design: Healthcare professionals, including community pharmacists, hospital pharmacists, nursing home physicians, general practitioners and geriatricians were recruited in the province of Limburg, the Netherlands.

Method: A research group, selected for their expertise in the field of medication reviews, established covariates that could possibly affect the quality of medication reviews. An electronic questionnaire, including these covariates, was developed and was subsequently sent to the participants who rated the covariates using a 10-point scale. Finally, the research group classified the scores. Physicians and pharmacists were evaluated jointly and separately to account for possible differences.

Results: 29 out of 49 participants completed the study. Thirteen covariates were evaluated and their medians and ranges were calculated. The five most important covariates were, from most to less important, knowledge of the indication for the drug, use of guidelines, reviewer's professional field, knowledge of the medical history, and use of laboratory values. Both groups found the indication for the drug the most important covariate.

Conclusion: We found that the most relevant covariates that may lead to a high-quality medication review are: drug's indication, use of patients' medical history, use of guidelines, reviewer's professional field, and use of laboratory values.

Introduction

Although it is a relatively new concept, the definition of a medication review and its different approaches have been extensively discussed during the last few years [1, 2]. Medication reviews are important for the quality of prescribing and prevention of adverse drug events. Christensen and Lundh state that even though no generally accepted definition exists, a medication review could be defined as "a systematic assessment of the pharmacotherapy of an individual patient that aims to evaluate and optimise patient medication by a change (or not) in prescription, either by a recommendation or by a direct change" [3].

Similarly, the Pharmaceutical Care Network Europe, defines medication reviews as an evaluation of patients' medicines with the aim of managing the risk and optimising the outcome of medicine therapy by detecting, solving and preventing drug-related problems [2].

Elderly patients often suffer from various diseases which frequently results in the use of multiple medicines. Polypharmacy bears an intrinsic risk for adverse drug reactions that may lead to hospitalisation and comorbidity [4]. Research on polypharmacy is mostly aimed at reducing merely the number of prescribed drugs, whereas the goal should be optimising the medication list, as reducing is just one of the multiple actions that can be taken during the medication review process. In addition, underprescribing is encountered in poly-pharmacy patients and paradoxically increases with the number of medicines already prescribed [5, 6].

The complexity and toxicity of some drugs highlight the necessity of using skills to promote adherence and compliance and to minimise harm and drug-related hospital admissions [7, 8]. This shows the present importance of medication reviews and its future expectations to improve patients' safety. Medication reviews are considered an essential element of high quality healthcare systems [8, 9], regarding elderly patients, polypharmacy and adverse drug reactions.

Most of the literature on medication reviews focuses on aspects such as discipline, experience of the reviewer, setting, automation possibilities and/or use of computerised methods [1, 4, 9-23]. Surprisingly, there is barely any literature concerning which information should be checked to perform a good medication review, how it should be performed or who should be responsible for it. From our point of view, determining what information leads to a high-quality medication review is the first step that should be performed before focusing on any other aspects. Notwithstanding, this is a controversial statement because it has never been properly investigated. Further, since different professionals have different infor-

mation to their exposure, it is interesting to see which information they find important when having to perform a medication review.

In the near future, we want to use these most important covariates as the basis of the development of a computerised decision support system, within the SCREEN project (Supporting Clinical Rules in the Evaluation of Elderly patients with Neuropsychiatric disorders), to support clinical practice in nursing homes and elderly care homes.

Aim

Given the lack of information concerning the factors that may influence the quality of medication reviews, this study was set to establish the relative importance of different covariates in order to perform a high-quality medication review, based on physician and pharmacist opinion.

Methods

Research group and selection of covariates

The research group consisted of 4 physicians and 4 pharmacists. Their expertise focuses on elderly care medicine, care for the elderly, chronic care, neuropsychiatry and old age psychiatry, pharmacotherapy and medication reconciliation. The research group, enumerated as many covariates as could be considered potentially relevant in performing a medication review. All the covariates were discussed in order decide which covariates should be included in the present study.

Creation of questionnaire based on the covariates

The research group developed an electronic questionnaire based on the covariates obtained via consensus. In the questionnaire, all the covariates were stated so that they could be rated by means of a 10-point scale, where 10 indicated most important and 1 least important for the quality of a medication review.

Participants' recruitment

Healthcare professionals including hospital pharmacists, community pharmacists, nursing home physicians, general practitioners and geriatricians within the Netherlands were recruited via phone and or email to participate in the project.

Questionnaire

The participants were asked to rate each of the covariates according to their importance for the quality of a medication review.

Questionnaire evaluation

The research group evaluated the results of the questionnaire. For each covariate, the median and the range were calculated. Physicians and pharmacists were evaluated jointly and separately to take into account possible differences between professional fields.

From a practical point of view, the research group established the top 5 covariates as having too much information could make the medication review process slower and tedious and too little information could lead to incorrect decision. It was agreed that these top 5 covariates will be further investigated to establish their real impact on medication reviews, and with a positive assessment these will be included in the supporting system within the SCREEN project. The rest of the covariates will be evaluated on a later phase of the project, with the possibility to be included in the supporting system after evaluating, when considered appropriate, their real impact on medication reviews.

Results

Covariates

The research group established thirteen covariates that were included in the questionnaire.

Participants

The questionnaire was sent to 49 healthcare professionals of whom 29 (59%) fulfilled the complete study; the other 20 professionals refused due to lack of time.

Among those who answered, there were 17 (59%) physicians and 12 (41%) pharmacists. From the 17 physicians, 3 (18%) were general practitioner, 9 (53%) were nursing home physicians and 5 (29%) were geriatricians. As for the pharmacists, 7 (58%) were community pharmacists and 5 (42%) were hospital-based pharmacists.

Evaluation

The covariates, as well as their overall classification, and the pharmacist specific and physician specific classification, are listed in table 1.

After the overall evaluation, the top 5 covariates, were knowledge of the indication for the drug (9), use of guidelines (9), reviewer's professional field (8), knowledge of the medical history (8), and use of laboratory values (8). The rest will be considered helpful covariates.

As presented in table 1, the scoring between pharmacist and physicians differed slightly but both groups found "indication for the drug" the most important covariate.

Table 1. Median scores and ranges from the general and field-specific classification of the covariates by using a 10-point scale.

	Total (n=29) Median (range)	Pharmacists (n=12) Median (range)	Physicians (n=17) Median (range)
Indication for the drug	9 (7-10)*	9 (3-10)	9 (7-10)
Use of guidelines	9 (3-10)*	9 (3-10)	8 (3-10)
Reviewer's professional field	8 (7-10)*	8 (7-10)	8 (7-10)
Use of patients' medical history	8 (5-10)*	8,5 (5-10)	8 (5-10)
Use of laboratory values	8 (4-10)*	8 (3-10)	9 (4-10)
Use of patients' characteristics	8 (3-10)	8 (3-10)	8 (5-10)
Knowledge of reason for admission	8 (3-10)	7,5 (3-10)	8 (3-10)
Number of drugs per patient	8 (1-10)	8 (1-9)	7 (1-10)
Patients' involvement	7 (3-10)	7,5 (4-10)	6 (3-10)
The use of structured methods	7 (1-10)	8 (7-10)	7 (1-10)
Nurse's involvement	6 (3-9)	6,5 (4-10)	5 (3-9)
The setting	6 (1-9)	5 (7-10)	6 (1-9)
Medium used to perform a medication review	6 (1-10)	6 (1-9)	6 (1-10)

* Top 5 covariates

Discussion

Previous studies have shown that adverse drug events are a common cause for hospitalisations and how medication reviews might have an impact on such kind of

hospitalisations [1, 8, 9, 24, 25]. In the HARM (Hospital Admissions Related to Medication) study, Leendertse et al. found that up to 46% of the drug-related hospital admissions were preventable; based on their findings they recommended the performance of regular medication reviews in order to improve that outcome [8]. By using the STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) screening tool, potentially inappropriate medicines as well as adverse drug events in the elderly were highlighted. The suggestions, and the later actions, that arose after using these criteria resulted in an increase of 11.5% in the detection of potential adverse effects of inappropriately prescribed medications that could cause or contribute to drug-related hospital admissions; for instance, avoiding prescribing an anticholinergic to treat extrapyramidal effects of neuroleptic medication in an older patient with dementia and behavioural symptoms [24].

Some studies give an idea of the covariates that should or could be checked to improve the quality of a medication review. The United States as well as Canada have explicit criteria for medications considered inappropriate in elderly patients [26, 27]. In Europe, the POM (Prescribing Optimisation Method) study focused on 6 questions which should be asked to optimise the prescribing system; the results showed an increase of the correct decisions proportion when prescribing [28]. Although the POM study and the present one have some points in common, the main difference between these studies lies in the study aim: prescribing optimisation system vs. importance of different covariates when performing a medication review.

The STOPP study established some criteria for the detection of potentially inappropriate medication significantly associated to avoidable adverse drug reactions that could cause or contribute to hospitalization [24]. Conjointly, the START (Screening Tool to Alert doctors to the Right Treatment) study validated a screening tool to systematically identify appropriate omitted medicines in polypharmacy older patients [6].

Some of these studies have used the Delphi method [6, 24, 26], however, we decided to use the described method instead to minimise the time expenditure of the healthcare professionals. A considerable number of professionals stated workload as a restriction to participate in this study. Therefore, and even though the Delphi method would have been an attractive alternative, it was considered to be too time consuming for them.

In addition, all these studies or criteria are aimed at supporting the medication surveillance, acting at different stages and obtaining different results; however, none of them studied if the used covariates were the correct ones in order to obtain an optimised system or result. Therefore, our approach in the present study

was to go this step backwards and evaluate which are the most important covariates to perform a medication review.

Given the results it is interesting to notice the limited differences between the physician's and the pharmacist's opinions; the most important considered covariate was the same one both for physicians and for pharmacists, namely the knowledge of the indication for each drug.

For the rest, even though there are mostly the same covariates, the order of importance differs, most probable due to the actual difference in availability of information for physicians and pharmacists when performing a medication review.

The fact that the available information varies might imply that medication reviews are currently done differently depending on the point of view of the different healthcare fields. This could lead to a bias when regarding the covariates since the point of view could be subjective according to what they perform on a daily base.

We can roughly say that the order in which covariates are ranked might depend on the different information that professionals have and the type of medication review that they are used to.

Establishing these covariates is the first step for the development of a complete computerised decision support system for the SCREEN project to support clinical practice in nursing homes and elderly care homes taking into account all the mentioned information to achieve, not only a high-quality medication review but also to make the medication review process less time-consuming. At the same time, the project will try to improve the quality of life for polymedicated patients and hopefully a decrease of unnecessary medication-related healthcare costs will be reported.

Further investigations are necessary to establish the real impact of the covariates on medication reviews.

Conclusion

We found that the most relevant covariates that may lead to a high-quality medication review are: drug's indication, use of patients' medical history, use of guidelines, reviewer's professional field, and use of laboratory values.

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Chapter 4

To what extent is clinical and laboratory information used to perform medication reviews in the nursing home setting? The CLEAR study

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To what extent are clinical and laboratory information used to perform a medication review in the nursing home setting? Therapeutics and clinical risk management 11 (2015): 767.

Abstract

Aim: To evaluate to what extent laboratory data, actual medication, medical history and/or drug indication influence the quality of a medication review for nursing home patients.

Methods: 46 health care professionals from different fields were requested to perform medication reviews for three different cases. Per case, the amount of information provided varied in three subsequent stages: stage 1) medication list only; stage 2) adding laboratory data and reason for hospital admission, stage 3) adding medical history/drug indication. Following a slightly modified Delphi method, a multidisciplinary team performed the medication review for each case and stage. The results of these medication reviews were used as reference reviews (gold standard). The remarks from the participants were scored according to their potential clinical impact from relevant to harmful on a scale of 3 to -1. A total score per case and stage was calculated and expressed as a percentage of the total score from the expert panel for the same case and stage.

Results: The overall mean percentage over all cases, stages and groups was 37.0% compared to the reference reviews. For one of the cases, the average score decreased significantly from 40.0% in stage 1, to 30.9% in stage 2, and 27.9% in stage 3; no significant differences between stages was found for the other cases.

Conclusion: The low performance, against the gold standard, of medication reviews found in the present study highlights that information is incorrectly used or wrongly interpreted, irrespective of the available information. Performing medication reviews without using the available information in an optimal way can have potential implications towards patients' safety.

Introduction

Polypharmacy is defined as the use of more than a certain number of drugs irrespective of their appropriateness [1-3]. In the Netherlands, it has been defined as the chronic use of five or more drugs from different therapeutic groups or subgroups [4].

According to the Foundation for Pharmaceutical Statistics (SFK Stichting Farmaceutische Kengetallen), on average, 10% of the pharmacy visitors in the Netherlands are polymedicated. As expected, this percentage increases with age. For patients under 40, between 41 and 64, between 65 and 69, between 70 and 74, and over 75 years the percentage of patients who are polymedicated was 0%, 8%, 20%, 25%, and 33%, respectively [5].

Polymedicated patients are at increased risk of both experiencing adverse drug reactions, and possibly undertreatment [6]. Frail and disabled nursing home patients with polypharmacy have an increased risk [1, 2]. In addition, the management of these patients is often complex because of organ function impairment and/or comorbidities [1-3, 7-9].

Developing and assessing new care interventions are the key to optimizing pharmacotherapy, and thus inhibiting the negative effects of polypharmacy [10]. Studies have suggested that the elements of a successful medication review include the use of a standardized method performed by pharmacists and physicians, as well as the use of laboratory data and a complete medical and drug history [11-16].

Computerized clinical decision support systems (CCDSS) can be defined as decision-aiding tools that provide health care professionals with clinical knowledge and patient-related information, intelligently filtered or presented at appropriate times, to enhance patient care [17-19]. Most of the current computerized systems are based on drug history and laboratory data but do not take into account the indication of the drug and/or the medical history [17, 20]. By not considering these factors, an important part of a medication review could be missed, as there is not any knowledge about the necessity for a drug to be prescribed or to be discontinued. This could lead to an unnecessarily increase of polypharmacy, or to underprescribing (e.g. in case of a patient with a history of myocardial infarction not using a statin or acetyl salicylic acid).

In a previous study, we demonstrated the importance of different covariates in order to perform a high-quality medication review [21]. We concluded that the most important covariates to consider were the medical history and/or drug indication, use of guidelines, the reviewer's profession, and the availability of laboratory data. Of these, medical history, drug history and laboratory data have also been recommended in other studies for their potential to lead to a successful medication review [11-16]. Therefore, these variables were selected for this study.

Objective

The present study evaluates to what extent different types of information (actual medication, reason for hospital admission, laboratory data, and medical history/drug indication) influence the quality of the review for nursing home patients.

Methods

A total of 85 participants were invited to participate in this study: 33 nursing home physicians, 30 community pharmacists, and 22 general practitioners. The idea was to have at least 15 participants per group in order to compare between the different professions. We included pharmacists and general practitioners, since different studies had suggested that pharmacist and general practitioner-led medication reviews could lead to a successful medication review, and we included nursing home physicians, because they have to deal with complex, frail elderly with relatively high prevalence of polypharmacy and our project SCREEN (Supporting Clinical Rules in the Evaluation of Elderly patients in Nursing homes) focuses on the nursing home setting [8, 9, 11, 14, 16, 22].

General practitioners, nursing home physicians and community pharmacists working in Limburg, in the south of the Netherlands, were asked to participate in the study. They were recruited via an electronic questionnaire in which the aim of the study and the study design were appropriately described, and their participation was requested. As an incentive to participate in the study, a complementary accredited course on the medication review topic was provided by IVM (Instituut voor Verantwoord Medicijngebruik, Institute for Responsible Medication Use) for the health care professionals after they had finished the reviews.

Vignettes of three cases were developed based on real nursing home patients with their complexity (polypharmacy and multimorbidity) [23]. A number of medical related problems were introduced in the medication list, laboratory values and/or medical history/drug indication. These medical related problems included medication without indication or indication without medication, contraindications, interactions and/or possible side effects, dosage problems, double medication or wrong medication. For each vignette, information was presented in three stages: in stage 1 only the medication list was presented, in stage 2 the reason for hospital admission and the laboratory results were added, and in stage 3 the complete dataset was presented, including the medical history and/or the indications of the drugs.

Using a slightly modified Delphi method, a multidisciplinary expert team, comprising hospital pharmacists (HvdK, BvO, RJ), hospital pharmacists in training (HdW, CM), a

geriatrician (WM), nursing home physicians (JS, KH), and a neuropsychiatrist (FV), performed the medication review for each case and stage previous to the start of the study, thus establishing a reference medication review as the gold standard. The experts used the current applicable clinical management guidelines. The experts reviewed the same case and stage at a time, and all remarks on the medication review were discussed, until consensus was reached. In addition, the multidisciplinary team scored each remark, from 0 to 3, based on the considered clinical relevance: 3 points for remarks of high clinical relevance, 2 points for remarks of moderate clinical relevance, and 1 point for remarks of low clinical relevance. It was agreed that on the participants' evaluation a score of 0 points would be given when no remark was made and a minus 1 point would be given for potentially harmful remarks.

In addition, a standardized answer form was developed for each case. This form consisted of a table with three columns: medication, remarks and actions. The structure of the design is illustrated in Figure I.

The different cases were presented to the participants in the following order:

Stage 1: Medication list only

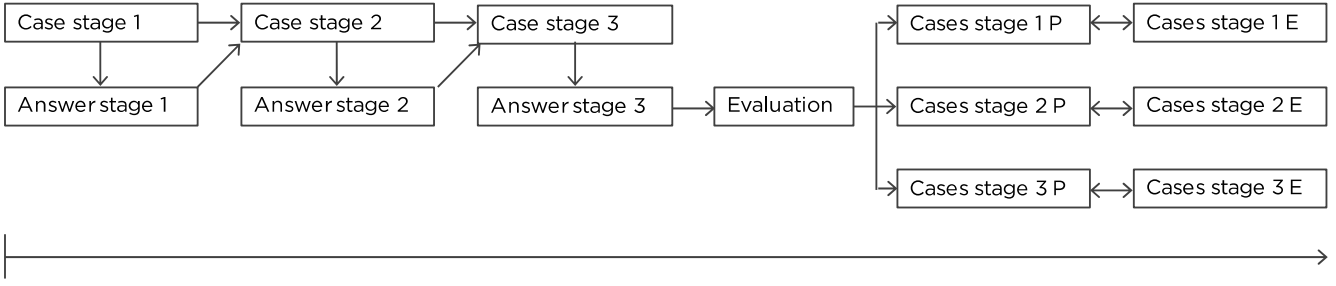
The vignettes of 3 cases were sent by email, together with a standardized answer form on which the participants were asked to note the potential problems with the medication that was on the list, as well as potential actions obtained from their medication review. In addition, participants could give suggestions to add or stop drugs according to their own opinion.

Stage 2: All information except from medical history/drug indication

Next, the same vignettes were sent again, in which data concerning laboratory values and reason for hospital admission was added. The participants also received the answer forms that they had completed in stage 1. In this way, we could see the changes in the outcome of the medication review, when they had access to the reason for hospital admission and the laboratory data.

Stage 3: All information

Finally, case reports, including the complete information set (medication list, laboratory data, reason for hospital admission and medical history/drug indication) were sent once more, together with the answer forms that the participants filled in for stage 2 to see again the changes in the outcome of the medication review.



Stage 1: with medication list only
Stage 2: all information (medication list, reason for admission and laboratory values) except drug indication and/or medical history
Stage 3: complete case (medication list, reason for admission, laboratory values, drug indication and/or medical history)

Figure I. Study and evaluation design (P = Participants and E = Expert team)

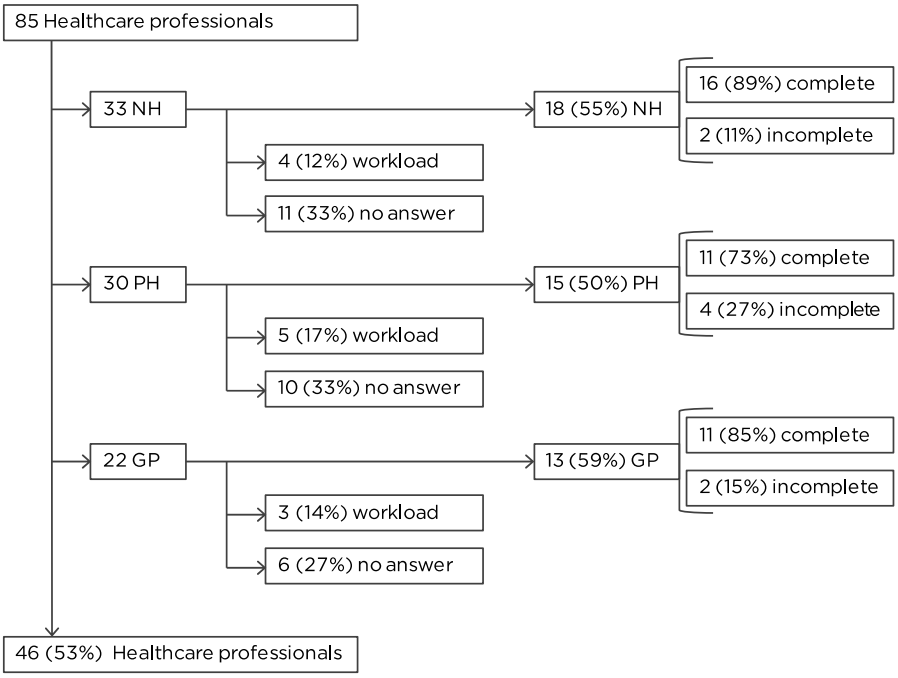
The answer forms that were returned were independently evaluated by 2 members of the expert team, who tried to reach consensus. The experts were not blind to the information participants had when evaluating their performance in the different stages. If their opinion on a remark diverged, a third member, acting like moderator, addressed the remark until consensus was reached. Per case, stage, and health care professional, a total score was obtained by comparing their remarks with the corresponding ones from the expert team, i.e. with the same available information, in order to assess the quality of the review, measured by the number and type of remarks made. If a participant made the same remark as the expert team, he/she got the same score for that remark; if the participant made no remark or an incorrect remark, a zero or a minus one score was given, depending on the potential harm such remark could cause.

In case a new remark, not proposed by the expert panel, would be encountered during the evaluation, the remark would also be taken into the gold standard, after being evaluated within the expert team. That remark would also get a score and all the cases would be rechecked for that specific remark.

The principal outcome measure was the relative score of the health care professional compared to the expert panel expressed in percentages of the score from the reference panel. For each case linear mixed models with an unstructured covariance structure for the repeated measures were used to assess the average trend over stages for all health care professionals as well as for each group separately, and the group effect at each stage. Linear mixed models were used to account for the correlations between repeated measurements within the same health care professional, and missing data, assuming the data to be missing at random (MAR). The analyses were corrected for participants that didn't fulfil the three stages. All analyses were performed using IBM SPSS Statistics for Windows (Version 19.0. Armonk, NY: IBM Corp).

Results

Of the 85 health care professionals who were approached, 46 (54.1%) participated in the study; from these participants, 38 (82.6%) fulfilled the study, 4 (8.7%) stopped after stage 1, and 4 (68.7%) stopped after stage 2. Figure II.



(NH = Nursing home physician, PH = Pharmacist, GP = General Practitioner

Figure II. Participation and dropped out percentages:

The demographic characteristics of the participants are on Table I. The results obtained for the three cases, by group and stage, are listed on Table II.

Table I. Demographic characteristics of the participants

PH	5 (33.3%) males
15 participants	10 (66.6%) females
	17,2 average years of experience
NH	6 (33.3%) male
18 participants	12 (66.6%) female
	13.4 average years of experience
GP	7 (53.8%) male
13 participants	6 (46.2%) female
	20.9 average years of experience

Table II. Estimated mean percentage ± standard error (SE) for cases A, B and C, differentiated by group and stage.

	Case A			Case B			Case C		
Group	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
All	40.0 ± 2.3*	30.9 ± 3.6*	27.9 ± 3.2*	38.0 ± 3.8	35.2 ± 3.7	36.4 ± 3.1	41.4 ± 2.6	40.3 ± 3.2	42.7 ± 3.2
PH	38.7 ± 4.0	40.1 ± 6.2#	30.2 ± 5.9	42.5 ± 6.6	42.1 ± 6.7	40.9 ± 5.7	42.2 ± 4.6	41.0 ± 6.0	39.6 ± 6.0
NH	37.1 ± 3.6‡	20.1 ± 5.4‡#	21.9 ± 5.0‡	29.9 ± 6.1	29.1 ± 5.9	33.1 ± 4.8	40.7 ± 4.2	45.1 ± 5.2	42.1 ± 5.0
GP	45.6 ± 4.2	36.3 ± 6.4	33.8 ± 5.9	44.2 ± 7.1	36.5 ± 6.6	36.0 ± 5.7	41.5 ± 5.0	33.9 ± 5.7‡	46.9 ± 6.0‡

(PH = Pharmacists, NH = Nursing home physicians, GP= General practitioners)

* Statistically significant for case A, the overall mean percentage significantly decreased over the stages (p=0.001). The mean differences decreased between stages 1 and 2 (-9.1, 95%CI -15.3, -3.0, p=0.005), and between stages 1 and 3 (-12.1, 95%CI -18.6, -5.6, p<0.001).

‡ Statistically significant within-group effect over the different stages found for case A from stage 1 to stage 2 (p=0.001), and from stage 1 to stage 3 (p=0.005) in group 2 (NH), and for case C from stage 2 to stage 3 (p=0.037) in group 3 (GP).

Statistically significant between-group effects for case A at stage 2, i.e. the estimated mean percentage was significantly lower in group 2 (NH) (20.1%) than in group 1 (PH) (40.1%, p=0.019).

The overall mean score for all cases, and stages was 37.0% for the total group of health care professionals, 39.3% for the pharmacists group, 32.9% for the nursing home physicians group, and 40.3% for the general practitioners group. The overall mean score for the three cases was 32.9%, 36.5% and 41.5%, respectively. For one of the cases, the overall mean percentage significantly decreased over the stages ($p = 0.001$): the mean differences between stages were as follows: between 1 and 2 (-9.1, 95%CI -15.3, -3.0, $p = 0.005$), and between stages 1 and 3 (-12.1, 95%CI -18.6, -5.6, $p < 0.001$). For the other two cases, no significant differences were found over the stages. As for the within-group effect over the different stages, no significant interactions between stage and group were found for the three cases. For one of the cases, significant decreases were found from stage 1 to 2 ($p = 0.001$), and from stage 1 to stage 3 ($p = 0.005$) in group 2 (NH). For another case, the mean percentage significantly decreased from stage 2 to stage 3 ($p = 0.037$) in group 3 (GP). As for the between-group effects, only a significant difference was found for one of the cases at stage 2, i.e. the estimated mean percentage was significantly lower in group 2 (NH) than in group 1 (PH) (20.1% vs. 40.1%, $p = 0.019$).

The results obtained for the different cases, groups and stages show low performance against the gold standard, irrespective of the available information. The highest score was 46.9% for one of the cases at stage three and from the general practitioners group (GP's). The lowest score was 20.1% for one of the cases at stage two and from the nursing home physicians (NH) group. The absolute percentage scores per participants were for stage I for PH, NH and GP's respectively 41.1 ± 3.6, 35.9 ± 3.3 and 43.8 ± 2.9; for stage II 41.1 ± 4.6, 31.4 ± 5.3 and 35.6 ± 4.9 respectively for PH, NH and GP's; and for stage III 36.9 ± 6.4, 32.4 ± 6.2 and 38.9 ± 6.7 respectively for PH, NH and GP's.

Medication related issues that were identified by a few participants included the addition of new medication (vitamin D, nitro-glycerine and ACE-inhibitor), and switching medication (switching bumetanide because of laboratory values and switching aspirin to acenocoumarol. Benzodiazepines related remarks were well identified (stopping or decreasing oxazepam / temazepam), together with remarks concerning dose reduction due to laboratory values or lack of indication (ferrous fumarate, haloperidol, opioids). There were no remarks that were either missed or noticed by all the participants.

Discussion

Given the frailty of patients which such profile, it is evident that a high-quality medication review is crucial. Overall, we found that only about 37% of the remarks that could potentially have been made, were actually raised by the participants. This

represents a low to moderate mean quality of these reviews, even though health care professionals were given the information that could potentially lead to a successful medication review according to previous studies [11-16].

For one of the cases a significant difference was found at stage 2 between pharmacists and nursing home physicians, scoring the last ones significantly lower. This difference could be explained due to the fact that pharmacists often don't have access to laboratory results and the moment they got this information extra attention would have been paid to perform the medication review. Also, for one of the cases having extra information resulted in a significant decrease of the overall mean percentage, while no clear reason can be seen, participants could have found this specific case more difficult in further stages.

Even though the recruitment and the communication with the participants was done electronically, the tight contact with these health care professionals in the region implies that the study was taken seriously and that the results reflect a real-life problem. In addition, the amount of time was no more than a total of 2 hours given the fact the same cases were sent only adding extra information.

During the evaluation, the two members of the expert team who evaluated the results and the moderator encountered three remarks (1.8%) that had not been made by the expert team. These remarks were once more discussed within the expert team and two of them were finally included in the gold standard. When evaluating the results, the moderator took action in approximately 10% of the cases, when the two independent members from the expert team did not reach consensus. In addition, and as explained in the methods section, minus 1 point was given for potentially harmful remarks. Examples of remarks that were scored with a minus one point were: not pointing out that the thiamazole dose should be decreased when the TSH was too high; not making any reference that there was an interaction or contraindication between Carbidopa/Levodopa and Haloperidol; not pointing out that the dosage for alendronic acid 70mg was once a day; or not seeing that the patient was allergic for penicillin and co-amoxiclav was prescribed.

In addition, the remarks that were more often missing concerned the addition of new and necessary medication, highlighting the paradoxical relationship between polymedicated patients and underprescribing [6].

Although no statistically significant differences were found for the vast majority of the situations (cases, stages and groups), the mean percentages found after the evaluation demonstrates that there is room for improvement by correctly using and interpreting the available information.

A limitation for this study is that the gold standard was established by a multidisciplinary team while the participants performed the medication review on their own. The fact that the expert team was a multidisciplinary team might have brought a

different perspective to the gold standard in terms of practice of clinical judgment. However, all the medication reviews were compared to one same gold standard and thus the possible differences are not expected to be different per group. This difference between multidisciplinary team as the gold standard versus individual judgment reflects also the benefit of such a collaborative, inter-disciplinary approach. This difference should be approached in a future study. Another limitation might have been the fact that there were no initial individual scores for the expert panel and thus they could not be compared with the final "gold standard". In this way, the different perspectives on clinical decision making might be missing. In addition, in this study patient interviews were not taken into account while in real life these patient meetings can have an influence on the medication review.

In a previous study, we evaluated which variables should be considered to perform a high-quality medication review [20]; in the present study, we have evaluated how such variables are interpreted.

Our final goal is to use these most important variables as the basis for the development of a CCDSS, within the SCREEN project [21]. This system is intended to support clinical practice in nursing homes, homes for the aged and other settings, making the clinical medication review process less time-consuming, decreasing unnecessary medication-related health care costs and improving the quality of life for older patients with polypharmacy. This system will include the previously suggested prerequisites for a high-quality medication review i.e. using a standardized method, in our case a CCDSS, which takes into account laboratory data, medical and drug history and which is developed and performed by a multidisciplinary team.

Conclusion

Clinician performance regarding medication reviews was less than ideal and there is need for better understanding for the reasons for such performance. This low performance, against the gold standard, of medication reviews found in the present study highlights that information is incorrectly used or wrongly interpreted, irrespective of the available information. Performing medication reviews without using the available information in an optimal way can have potential implications towards patients' safety. In addition, a team approach may have had a greater impact and perhaps such an interdisciplinary is also a solution to improving the quality of medication reviews.

These results stress that there is room for improvement and the possible necessity of a transition towards a combined medication review using the current medication

review system, handmade performed medication review, supported by a computerized clinical decision support system.

In a future study, the impact of using a computerized clinical decision support system in daily nursing home care practice will be established.

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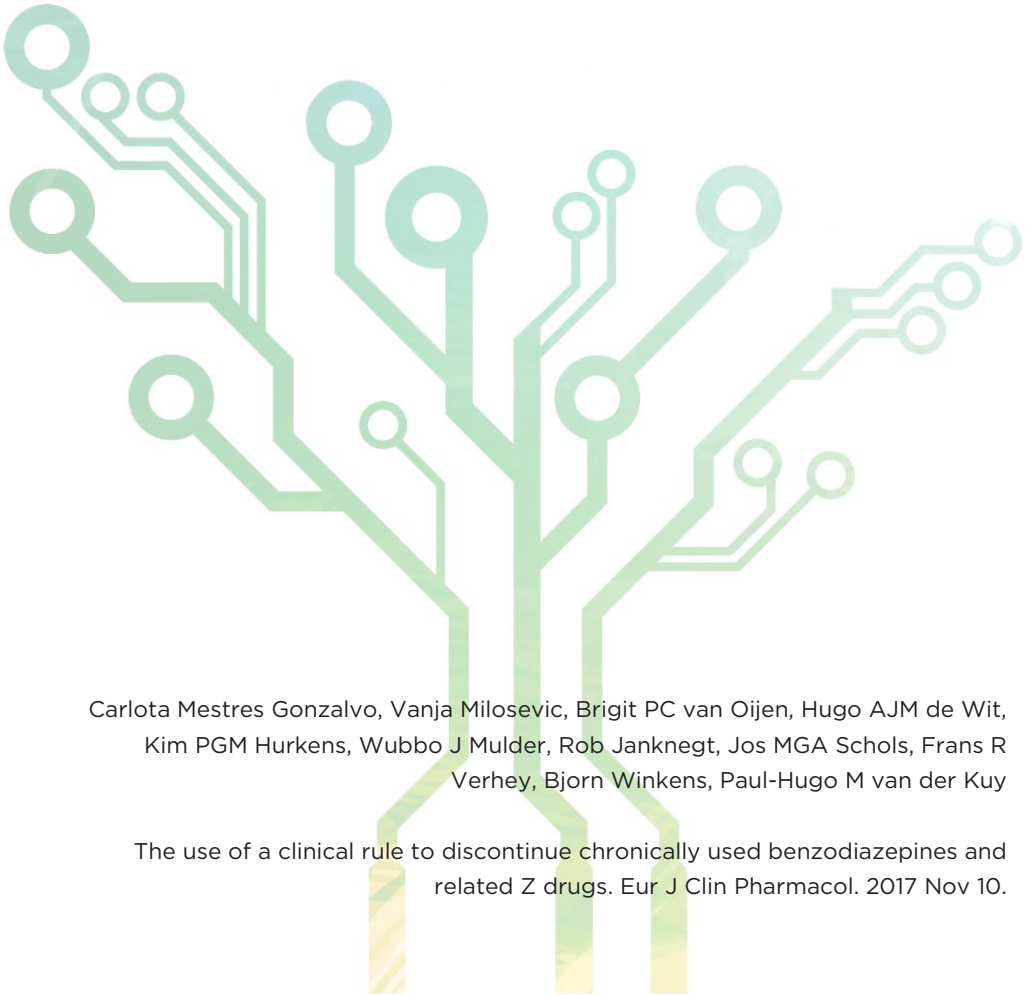
Chapter 5

The use of a clinical rule to discontinue chronically used benzodiazepines and related Z drugs



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The use of a clinical rule to discontinue chronically used benzodiazepines and related Z drugs. Eur J Clin Pharmacol. 2017 Nov 10.

Abstract

Purpose: The chronic use of benzodiazepines and benzodiazepine-related drugs (BZ/Z) in older people is common and not without risks. The objective of this study was to evaluate whether the implementation of a clinical rule promotes the discontinuation of chronically used BZ/Z for insomnia.

Methods: A clinical rule, generating an alert in case of chronic BZ/Z use, was created and applied to the nursing home (NH) setting. The clinical rule was a one-off intervention, and alerts did not occur over time. Reports of the generated alerts were digitally sent to NH physicians with the advice to phase out and eventually stop the BZ/Z. In cases where the advice was adopted, a follow-up period of 4 months on the use of BZ/Z was taken into account in order to determine whether the clinical rule alert led to a successful discontinuation of BZ/Z.

Results: In all, 808 NH patients were screened. In 161 (19,1%) of the patients, BZ/Z use resulted in a clinical rule alert. From these, the advice to phase out and stop the BZ/Z was adopted for 27 patients (16.8%). Reasons for not following the advice consisted of an unsuccessful attempt in the past (38 patients), patients' family and/or patient resistance (37 patients), the non-continuous use of BZ/Z (32 patients) and indication still present (27 patients). Of the 12 NH physicians, 7 adopted the advice.

Conclusions: The success rate of a clinical rule for discontinuation of chronically used BZ/Z for insomnia was low, as reported in the present study. Actions should be taken to help caregivers, patients and family members understand the importance of limiting BZ/Z use to achieve higher discontinuation rates.

Introduction and objective

Benzodiazepines and benzodiazepine-related drugs (BZ/Z) are widely used to symptomatically treat insomnia [1]. Given their risks (i.e., dependence, tolerance and central side effects), their use should be limited to a maximum of 1 to 2 months, depending on the drug [2-7]. However, in daily practice, BZ/Z chronic use is widespread, especially within the nursing home population. European studies show a prevalence of chronic BZ/Z use in the nursing home population of between 28 and 50% [8-12].

Furthermore, based on different criteria, such as the Beers or the STOPP/ START criteria (screening tool of older people's prescriptions (STOPP) and screening tools to alert to the right treatment (START)), benzodiazepines have been identified as inappropriate medications; they should be avoided in patients 65 years and older, independent of diagnosis or condition. The reasons for this are the increased risks of impaired cognition, delirium, falls, fractures, and motor vehicle accidents with benzodiazepine use [1, 13, 14]. The STOPP criteria also suggest that benzodiazepines should not be used for longer than 4 weeks [14].

Given the importance of the earlier described events, a clinical rule was created to generate an alert whenever a patient used a BZ/Z for longer than 4 weeks, as described in the Summary of Product Characteristics (SPC) and the STOPP criteria [14]. A clinical rule is a real-time decision support module that focuses on medication safety and medication optimisation [15].

The objective of this study was to evaluate the feasibility of using a clinical rule to promote the discontinuation of chronically used BZ/Z for insomnia in the nursing home setting.

Methods

This feasibility study was performed in the Zuyderland nursing homes, which include 15 nursing homes with a capacity of approximately 800 patients. Patients admitted into one of the nursing homes in July 2016 were included in the study. In the present study, the clinical rule was applied as a one-off intervention.

A clinical rule was created to generate a report whenever a patient had been using a BZ/Z for longer than 4 weeks. An extraction of the medication information (drug, dosage, start date and stop date) was obtained using Crystal Reports, version XI, by SAP SE (Germany); Crystal Reports is a business intelligence application used to design and generate reports from a wide range of data sources. The clinical rule screened the extraction and generated a report creating an alert for patients who

had used a BZ/Z for longer than 4 weeks. For these patients, the indication of BZ/Z was established afterwards by taking into account the information on the medication record and/or the time the medication was given, assuming that a single night dose was indicated to treat insomnia. Establishing the indication was performed manually by medication record review by two of the authors (CMG and VM).

An advisory for each patient was generated whenever a patient had chronically been using BZ/Z. After the indication was assessed, these advisories were digitally sent to the respective nursing home (NH) physician (n=12) as a list. The advisory consisted in a recommendation for phasing out BZ/Z use and eventually stopping it. After the BZ/Z has been completely stopped, a minimum of 2 weeks resting period should be granted before evaluating whether there was still an indication for BZ/Z usage.

The NH physicians were requested to indicate whether the advisory to phase out BZ/Z and eventually stop it was followed or not. When the advisory was not adhered to, they were asked to specify the reason by indicating one of the following options:

- Patient/Family resistance
- It has already been tried before without success
- It is not necessary: BZ/Z use is only as needed
- Indication is still present

The NH physicians returned the digital list along with a reply to the question of whether they had followed the given advisory. Follow-up on BZ/Z use was performed during the period 4 months after the NH physicians had reacted in order to evaluate whether, in cases of following the advisory, BZ/Z had been successfully stopped.

Results

The clinical rule screened 808 NH patients, 269 (33.3%) of whom were using BZ/Z. Of these, 161 (19.9%) were chronically using BZ/Z to treat insomnia (i.e., longer than 4 weeks). The clinical rule generated 180 alerts, which means that 19 patients were using two BZ/Zs.

An advisory per patient was sent to the corresponding NH physician; only 27 out of 161 (16.8%) of the given advisories were followed, meaning that the NH physician had started phasing out the BZ/Z. The other 134 advisories (83.2%) were not followed by the NH physician. Figure 1 shows the inclusion and the follow-up for the given advisories.

The median time a BZ/Z was prescribed before the advisory was given was 19.1 months. This median time-use was slightly longer for the group in which the advisory was not followed (22.3) and was shorter for the groups in which the advisory was followed, i.e., being successfully stopped or restarted (17.2 and 14.8 resp.).

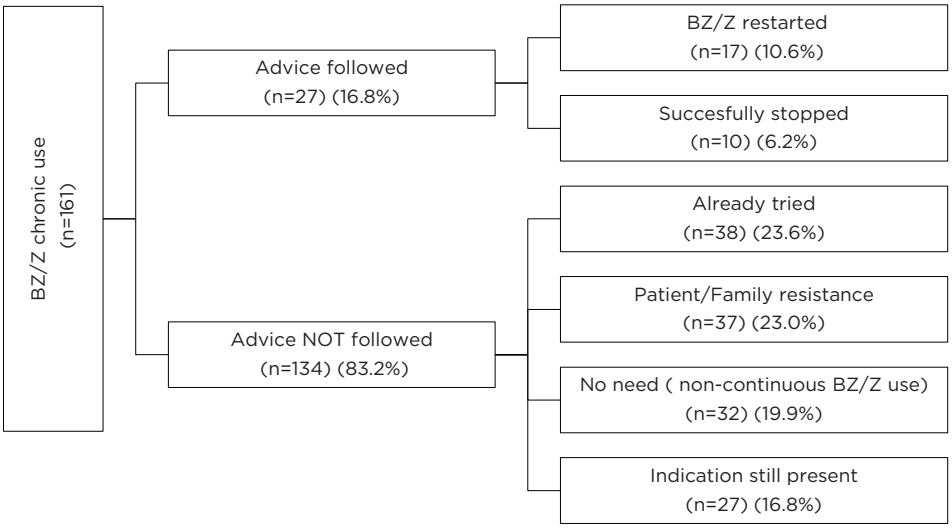

Figure 1. Inclusion and follow up

Baseline characteristics, including age, gender, time-use BZ/Z, and type BZ/Z are shown in table 1.

Regarding physician performance, 5 NH physicians did not follow any of the advisories to stop BZ/Z prescribing. The other 7 NH physicians adopted the advisory in 9.1% to 65.0% of their patients.

The most frequently used BZ/Z was oxazepam, followed by temazepam. In the group in which the advisory was adopted, the use of temazepam was higher than oxazepam (table 1).

Table 1. Baseline characteristics and time-use of the BZ/Z before intervention

	BZ/Z chronic use (n=161)	Advice NOT followed (n=134)	Advice followed	
			BZ/Z restarted (n=17)	BZ/Z stopped (n=10)
Mean age (SD)	84.4 (9.3)	84.5 (9.7)	85.8 (8.2)	83.8 (7.7)
Woman	125 (77.6%)	105 (78.4%)	14 (82.4%)	6 (60.0%)
BZ/Z time-use in months before intervention				
Median (IQR)	19.1 (81.7)	22.3 (81.3)	14.8 (9.1)	17.2 (9.5)
Max	92.5	92.5	27.2	46.5
Min	6.4	6.4	7.8	8.1
BZ/Z types (n)				
Alprazolam	1	1	0	0
Clorazepate	1	1	0	0
Flunitrazepam	1	1	0	0
Lormetazepam	1	1	0	0
Clobazam	2	2	0	0
Diazepam	4	4	0	0
Zolpidem	4	4	0	0
Nitrazepam	8	5	1	2
Zopiclone	17	14	1	2
Temazepam	50	39	8	3
Oxazepam	72	62	7	3

Discussion and conclusion

In the current study, the feasibility of a CR to discontinue chronically used BZ/Z for insomnia has been evaluated. Based on the data, we can conclude that even though it is feasible to discontinue chronically used BZ/Z drugs in the nursing home population, the success rate of the CR seems rather low. These results match with previous studies showing that in the nursing home population, BZ/Z discontinuation is difficult due to a lack of life prospects [12].

In the study of Burgeois et al, in 28% of the cases, discontinuation was initiated, and after 8 months of follow-up, 66.0% of the cases had successfully discontinued the use of BZ/Z. In the present study, in only 16.8% of the cases was discontinuation initiated, and at 4 months follow-up, 37% were successfully discontinued [12]. This can be explained by the fact that the time-use of BZ/Z in the current study was rather long, ranging from 6.4 months to 92.5 months. We strongly believe that the long time-use of BZ/Z in the present study made it more difficult to discontinue use. Furthermore, the prevalence of chronic BZ/Z use in the present study was 19.1%, which is on the lower side compared with the European prevalence of 28% and 50%. In addition, in the present study, it seems that when discontinuation of BZ/Z is started, the success rate to completely discontinue a BZ/Z increases when the resting period of 14 days is granted, as described in the STOPP criteria [14].

In the current study, the main reason not to adopt the advisory to discontinue a BZ/Z was the occurrence of an unsuccessful attempt in the past. This fact has not been checked in the present study, which is a limitation; nevertheless, another study mentioned the time needed to attempt the discontinuation process as a barrier to actually start the process [16]; this might explain why physicians in the present study seemed reluctant to start the discontinuation process again when it had already been (unsuccessfully) tried in the past, since it would mean a substantial time investment. The second reason was patient and/or family resistance; this finding is consistent with those of other studies, which mentioned patient resistance as an important factor working against chronic BZ/Z discontinuation [16-18]. These findings indicate that motivation and resistance, both from patients and family, seem to be the main reasons for low success rates. The present study consisted of a one-off intervention, and alerts did not occur over time; therefore, more research is needed to evaluate whether the success rate would be higher when alerts would be repeated occasionally (e.g., 2-3 weeks). In addition, and taking into account that the time-use for BZ/Z was rather long, more research is needed to evaluate if an alert, given directly after 4 weeks of BZ/Z use, would increase the success rate.

In the current study, no advice regarding a method to discontinue the BZ/Z was provided to the physicians. Other studies have given indications on how to best approach the process, including barriers and enablers [19, 20]. In addition, the clinical rule in the present study was a simple rule identifying patients who qualified for discontinuation. A more sophisticated algorithm could provide better results [21].

Even though the success rate for discontinuance of chronically used BZ/Z described in the present study was rather low, a simple clinical rule, which screens all NH patients within 5 minutes, can be used to identify which patients qualify for discontinuation. Further research is needed to evaluate ways in which the CR could be improved and/or how often and in which way the advice should be given to achieve a higher success rate. In addition, actions should be taken to help caregivers, patients, and family members understand the importance of limiting BZ/Z use in order to achieve higher discontinuation rates.

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Chapter 6

Validation of an automated delirium prediction model (DEMO delirium model): an observational study

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Abstract

Objectives: Delirium is an under-diagnosed, severe, and costly disorder, and 30-40% of cases can be prevented. A fully automated model to predict delirium (DEMO) in older people has been developed, and the objective of this study is to validate the model in a hospital setting.

Setting: Secondary care, one hospital with two locations

Design: Observational study

Participants: The study included 450 randomly selected patients over 60 years of age admitted to Zuyderland Medical Centre. Patients who presented with delirium upon admission were excluded.

Primary outcome measures: Development of delirium through chart review.

Results: A total of 383 patients were included in this study. The analysis was performed for delirium within 1, 3 and 5 days after a DEMO score was obtained. Sensitivity was 87.1% (CI: 0.756 to 0.939), 84.2% (CI: 0.732 to 0.915), and 82.7% (0.734 to 0.893) for 1, 3, and 5 days, respectively, after obtaining the DEMO score. Specificity was 77.9% (0.729 to 0.882), 81.5% (0.766 to 0.856) and 84.5% (0.797 to 0.884) for 1, 3, and 5 days, respectively, after obtaining the DEMO score.

Conclusion: DEMO is a satisfactory prediction model but needs further prospective validation with in-person delirium confirmation. In the future, DEMO will be applied in clinical practice so that physicians will be aware of when a patient is at an increased risk of developing delirium, which will facilitate earlier recognition and diagnosis, and thus will allow the implementation of prevention measures.

Introduction

A delirium or acute confused state is a transient attention and cognition disorder that develops over a short period of time and occurs mainly in hospitalised patients and people aged 60 years and over. Delirium is an under-diagnosed, severe (increased mortality), costly and often preventable disorder [1-3]. Its severity and symptoms can vary considerably, but the main features are impaired cognitive and sensory functions, reduced consciousness, and diminished attention. In addition, it is often accompanied by problems with psychomotor activity, the circadian rhythm, and emotions.

The prevalence and incidence of delirium in the general population differ widely depending on the setting. The overall prevalence in the community is estimated to be 1-2%. In a hospital setting, this prevalence increases to 10-31% at the time of hospital admission and 3-29% during hospitalisation. The incidence increases up to 87% when more specialised populations, such as the elderly and people in postoperative, intensive care and/or palliative care, are considered [4-11]. In 30-40% of cases, delirium is preventable, which, along with its associated high costs (ranging from US$164 billion to US$182 billion per year), makes it a perfect target for interventions by healthcare professionals [1, 4, 12-15]. As a result, a great number of screening tools have been developed and are widely used to detect the early onset of delirium, which can in turn allow treatment measures to be introduced in a timely manner [16-21]. These tools help healthcare professionals to establish and quantify symptoms associated with delirium [19-23]. Once the diagnosis has been established, the underlying medical condition can be targeted, and delirium can be managed appropriately.

There is no effective treatment for delirium [24, 25]. Preventing delirium is by far a more effective strategy to improve patient outcomes [1, 4, 26-29]. Risk models have been used to identify patients at higher risk for delirium development because these patients would most likely benefit from delirium prevention. These models are based on manual evaluation of individual risk factors and may be difficult to implement, so automated models are preferable and more feasible [30-34].

Screening instrument

A fully automated model to predict delirium in older people (over 60 years) was developed at Zuyderland Medical Centre. This DElirium MOdel (DEMO) uses only electronically available data to predict the occurrence of delirium. The predictive variables include age; polypharmacy; and the use of anti-dementia drugs, antidepressants, anti-Parkinson's agents, anti-diabetic drugs, analgesia and/or sleeping tablets (see Table 1). This model can be applied hospital-wide and has an area under receiver

operating characteristic (AUROC: measure for model prediction quality) value of 0.770 (95% CI 0736-0804) with a sensitivity of 78.2% and a specificity of 63.7%, when 14.1% is used as a cut-off value for the predicted probability of developing delirium. DEMO was developed retrospectively but has not yet been validated [4].

Therefore, the objective of this study is to validate DEMO in a hospital setting. To do so, the system's accuracy (main study parameter), i.e., sensitivity (proportion of delirium patients who test positive) and specificity (proportion of non-delirium patients who test negative), will be calculated. In addition to these parameters, the positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR+, LR-) with their 95% CI will be computed.

Table 1. DElirium MOdel and cut-off point

DEMO-score = 1/ (1+e- (Linear predictor))
DEMO score > 14.1% → Increased risk at delirium DEMO score ≤ 14.1% → No increased risk at delirium
Linear predictor = -8.823 + (0.081*V1) + (0.031*V2) + (0.248*V3) + (1.123*V4) + (0.286*V5) + (1.963*V6) + (0.359*V7) + (1.199*V8) + (0.413*V9) + (0.103*V10)
V1 = Age (years) V2 = Polypharmacy (number of drugs) V3 = Anxiolytics (ATC N05B) V4 = Anti-dementia (ATC N06D) V5 = Antidepressants (ATC N06A) V6 = Anti-Parkinson drugs (ATC (N04) V7 = Antidiabetic's (ATC A10) V8 = Antipsychotics (ATC N05A) V9 = Analgesics (ATC N02A) V10 = Sleep medication (ATC N05C)

* (ATC) Anatomical Therapeutic Chemical classification system (https://www.whocc.no/atc_ddd_index/)

Methods

This is an observational study of the ability of DEMO to predict delirium in an elderly hospital population. It was conducted in Zuyderland Medical Centre (locations Sittard and Heerlen) in the period from January 2016 to October 2016. The medical ethics committee METC Z (Medisch Ethische Toetsings Commissie van Zuyderland en Zuyd Hogeschool, Zuyderland Medical Centre, Heerlen) approved this study.

DEMO involves a daily analysis of all hospitalised patients ≥ 60 years of age at the different wards and predicts whether a patient is at risk of developing delirium in a 24-hour post-analysis period. The EPR (Electronic Patient Record) was accessed at a later date to check for delirium diagnosis. In this study, DEMO was calculated prospectively, but the outcome was ascertained by chart review retrospectively.

Although delirium diagnosis was determined by chart review, delirium documentation in our hospital is robust. At admission, patients are routinely screened for delirium, both in the emergency department and in the ward. The first screening is performed by a checklist (IGZ Inspectie voor de Gezondheidszorg = Dutch Healthcare Inspectorate, VMS Veiligheidsmanagementsysteem = Safety Management System, and Dutch guideline for delirium) [35, 36]. This checklist consists of 3 questions: does the patient need help with self-care?, has the patients previously suffered a delirium?, does the patients suffer from memory disorders?. When one of the questions is positively answered, the patient is at risk of developing delirium; in this case the DOSS (Delirium Observation Screening Scale) method [20] is used to evaluate whether a patient has delirium and it is subsequently noted in the chart.

Patients over 60 years who were admitted to Zuyderland were eligible for enrolment. From all patients admitted between 31-12-2015 and 31-10-2016, 450 patients were randomly selected (using https://www.randomlists.com-/team-generator) and their charts extracted for review. Patients who, based on chart review, presented with delirium upon admission were then excluded (Figure 1).

A search in the EPR was performed according to patient and date by using the following search terms: “delirium”, “delirious”, “agitation”, “agitated”, “confused”, “confusion”, “restlessness”, “disturbed”, “disorientation”, “disoriented”, “apathy”, “hallucination”, “mistrust”, “haloperidol”, and “delirium prevention measures”. These search terms were discussed with an internist geriatrician, a professor of geriatric medicine and a professor of geriatric psychiatry.

The search was performed by first identifying where the different words appeared in the EPR, and then, if any of these words appeared, the whole EPR during the admission period was read and interpreted by two authors (KH (internist geriatrician) and CMG (hospital pharmacist)) to determine whether it was truly a delirium diagnosis. All notes were reviewed, including notes by physicians, nurses, physiotherapists, and speech therapists. During the study, treating healthcare professionals (physicians, nurses etc.) were blinded to DEMO scores in order to avoid bias. If a diagnosis of delirium could not be established for a patient as a result of insufficient information in the chart, this patient was excluded from the analysis. The date of delirium onset was determined by chart review.

Delirium diagnosis based on chart review was then compared with the risk score from DEMO. The DEMO was dichotomized into two groups: high risk $\geq$ 14.1% [4], and low risk <14.1% for this analysis.

A two-by-two table was then constructed to calculate True Positive (TP), True Negative (TN), False Positive (FP), and False Negative (FN) rates.

The predictive value of DEMO was determined for delirium developing within 1, 3, and 5 days after the DEMO score was calculated. It had been developed to predict

delirium within the next 24 hours, but here we wished to also investigate whether its predictive value could be extended to three or five days.

In the study, wherein the DEMO was developed, an incidence rate of 17.4% was used [4]. Given the assumption of the same sensitivity of 0.75 (75%), we calculated that 33 delirium patients were needed based upon the requirement that the lower limit of 95% CI would be at least 60% (width of 95%CI ≤ 0.30 (30%)). With regard to the specificity, the number of non-delirium patients would be much larger than the number of delirium patients, and hence, the width of the 95% confidence interval (CI) for specificity would be smaller than 0.30.

It was assumed that at least 332 patients would be needed to identify 33 delirium patients. Taking into account the exclusion criteria and the possibility of a smaller percentage of patients who would develop delirium, a sufficient number of patients were screened to obtain 33 delirium patients (i.e., 450 patients).

The sensitivity, specificity, PPV, NPV, LR+, LR- with corresponding 95% confidence intervals were calculated with the use of an online calculator (http://vassarstats.net/clin1.html). The differences in PPV and NPV over time were tested using McNemar's test. The differences in age and gender between delirium and non-delirium groups were tested by using the independent-samples t-test and chi-square test, respectively. IBM SPSS statistics for Windows (version 23.0) was used to perform these tests. A two-sided p-value smaller than or equal to 0.05 was considered statistically significant.

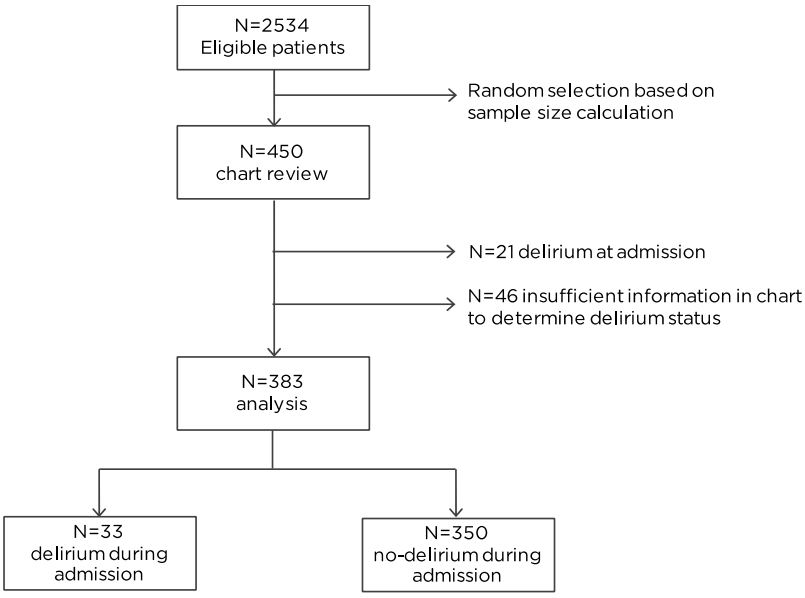

Figure 1. Flow diagram inclusion

Results

The study lasted eight months, for 450 patients chart review was undergone. Finally, a total of 383 patients were included, as 21 patients presented with delirium at admission, and for 46 patients there was insufficient information to determine delirium status (Figure 1). The results of the diagnostic test (TP/FP/FN/TN) for 1, 3 and 5 days after DEMO analysis are shown in Table 2. The analysis, including prevalence estimates, sensitivity, specificity, PPV, NPV, and likelihood ratios, is presented in Table 3. Although sensitivity decreased and specificity increased if the period increased from 1 day to 3 or 5 days after DEMO score was obtained, all values were rather high (sensitivity ≥ 0.827, specificity ≥ 0.779). PPV was statistically different $p < 0.001$ for all three comparisons (1 vs 3 days, 1 vs 5 days, 3 vs 5 days), NPV was not statistically different $p = 0.25, 0.004, 0.031$ for 1 vs 3 days, 1 vs 5 days and 3 vs 5 days, respectively.

Patients who developed delirium within 5 days were significantly older (mean age 83.9 (SD 7.8)) compared to those who did not develop a delirium within 5 days (mean age 73.9 (SD 9.1); $p < 0.001$). There was no significant difference in the percentage of males within the delirium and non-delirium groups (50.0% versus 50.1%, p=0.911).

Table 2. Test results of the prediction model (DEMO positive or negative) and diagnosis (delirium during admission or no-delirium during admission) within 1, 3 and 5 days after DEMO analysis.

	Delirium within 1 day after DEMO	No-delirium within 1 day after DEMO	Delirium within 3 days after DEMO	No-delirium within 3 days after DEMO	Delirium within 5 days after DEMO	No-delirium within 5 days after DEMO
DEMO Positive	54	71	69	56	81	44
DEMO Negative	8	250	11	247	17	241

Table 3. Estimates of the prevalence, sensitivity, specificity, PPV, NPV, and likelihood ratios with corresponding 95% confidence intervals 1, 3 and 5 days after DEMO analysis.

	Day 1 after DEMO analysis			Day 3 after DEMO analysis			Day 5 after DEMO analysis		
	Estimated value	95% confidence interval		Estimated value	95% confidence interval		Estimated value	95% confidence interval	
		Lower limit	Upper limit		Lower limit	Upper limit		Lower limit	Upper limit
Prevalence	16.2%	0.127	0.204	18.8%	0.150	0.221	25.6%	0.213	0.303
Sensitivity	87.1%	0.756	0.939	84.2%	0.732	0.915	82.7%	0.734	0.893
SpecificitySpecifitity	77.9%	0.729	0.822	81.5%	0.766	0.856	84.5%	0.797	0.884
PPV	43.20%*	0.345	0.524	51.3%*	0.419	0.607	64.8%*	0.557	0.730
NPV	96.90%	0.938	0.986	95.7%	0.922	0.977	93.4%	0.895	0.960
LR +	3.938	3.140	4.939	4.560	3.526	5.898	5.354	4.020	7.129
LR -	0.166	0.087	0.317	0.193	0.112	0.332	0.205	0.133	0.316

***PPV: Statistically different $p < 0.001$ for all three comparisons (1 vs 3 days, 1 vs 5 days, 3 vs 5 days)

DISCUSSION AND CONCLUSION

In the current study, a previously developed model for predicting delirium has been validated. DEMO was calculated prospectively, and the outcome was ascertained by chart review retrospectively. Based on the current data and the high sensitivity and specificity, it can be concluded that DEMO is a satisfactory prediction model.

Another strength of DEMO is that it predicts delirium within 5 days post-analysis on a daily basis. This is a novel concept, as most delirium prediction rules apply at admission but not daily. Even though it is not clear whether there is a definite advantage to predicting delirium on a daily basis, as this could lead to information overload, it could eventually be something that is tracked along with vital signs and intake/output.

We found sensitivity and specificity rates that were higher than reported in the study of de Wit et al., which may be because his study only checked the patients' medical history for delirium and not the entire EPR. Moreover, de Wit et al. had performed the search merely on the diagnosis of delirium. In the current study, the full EPR during the admission period was taken into account, and a wider set of terms was considered for delirium diagnosis. Furthermore, in the current study, in those cases in which delirium was not clear, these patients were excluded, whereas such patients had been included in the development of the delirium model [4].

The present study does present some limitations. First, the validation of the DElirium MOdel depends on how and when a healthcare professional reports that a patient has developed delirium. It is well known that documentation of delirium is poor since the majority of delirium remains unrecognised by clinical teams [37]. We therefore performed a wider search considering other words that might suggest delirium as delirium diagnosis and read through the whole EPR during the admission period. The number of delirium patients is noticeably higher than originally found, which can be explained by the search we performed. The DEMO is merely an aid to detect delirium, not a diagnostic tool by itself. Furthermore, for 46 patients there was insufficient information in the chart to determine delirium status, which could influence the generalisability of the present study.

In addition, as mentioned in the study by Inouye et al. [38], using a chart review method has some limitations as it has a 30% false positive rate and thus it is possible that patients with delirium at admission may have been included in the non-delirious cohort due to poor documentation in the chart.

Furthermore, the checklist used to screen the patients is a non-validated tool. Nevertheless, after that first check, the DOSS is used. The DOSS method is a validated method used by nurses to screen for delirium. Its sensitivity ranges from 89-100% and its specificity ranges from 88 to 96.6% [20, 39, 40]. The DOSS scores and its

conclusion (delirium/non-delirium) are recorded in the chart. In that way, and taking into account that the chart is a complete document in which different healthcare professionals note their findings, makes the outcome more reliable and strengthens the validity of the present study.

Another limitation of the present study is that this is a single-centre study (two hospital locations) located in the Netherlands and may not be generalisable in other settings.

The DEMO uses only electronically available data. Other important factors that could predict a delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model because they were not electronically available. If these data were also made electronically available, the predictive quality of DEMO could be improved [22, 23, 27, 30]. Taking into account that the registration of such factors is becoming increasingly important and mandatory, it is only a matter of time until these important factors can be used in the DEMO [2, 3]. In addition, DEMO already uses an alternative way of identifying cognitive impairment by including medications used for dementia.

The DElirium MOdel is a fully automated satisfactory prediction model that predicts delirium up to 5 days after analysis. The next step is to validate the DEMO in a cohort in which the outcome of delirium would be prospectively assessed in person and to use DEMO for retrospective measurements. In the future, DEMO will be applied to clinical practice so that physicians are alerted when a patient is at increased risk of developing delirium. This will facilitate earlier recognition and diagnosis and, thus, the implementation of prevention measures.

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Chapter 7

Supporting clinical rules engine in the adjustment of medication (SCREAM): protocol of a multicentre, prospective, randomised study

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Abstract

Background: In the nursing home population, it is estimated that 1 in every 3 patients is polymedicated and given their considerable frailty, these patients are especially prone to adverse drug reactions. Clinical pharmacist-led medication reviews are considered successful interventions to improve medication safety in the inpatient setting. Due to the limited available evidence concerning the benefits of medication reviews performed in the nursing home setting, we propose a study aiming to demonstrate a positive effect that a clinical decision support system, as a health care intervention, may have on the target population. The primary objective of this study is to reduce the number of patients with at least one event when using the clinical decision support system compared to the regular care. These events consist of hospital referrals, delirium, falls, and/or deaths.

Method/Design: This study is a multicentre, prospective, randomised study with a cluster group design. The randomisation will be per main nursing home physician and stratified per ward (somatic and psychogeriatric). In the intervention group the clinical decision support system will be used to screen medication list, laboratory values and medical history in order to obtain potential clinical relevant remarks. The remarks will be sent to the main physician and feedback will be provided whether the advice was followed or not. In the control group, regular care will be applied.

Discussion: We strongly believe that by using a clinical decision support system, medication reviews are performed in a standardised way which leads to comparable results between patients. In addition, using a clinical decision support system eliminates the time factor to perform medication reviews as the major problems related to medication, laboratory values, indications and/or established patient characteristics will be directly available. In this way, and in order to make the medication review process complete, consultation within healthcare professionals and/or the patient itself will be time effective and the medication surveillance could be performed around the clock.

Background

Polypharmacy is defined as the use of more than a certain number of drugs irrespective of their appropriateness [1, 2]. In the Netherlands, it has been defined as the chronic use of 5 or more drugs from different therapeutic groups or subgroups [3]. In the nursing home population, it is estimated that 1 in every 3 patients is polymedicated [4] and given their considerable frailty, these patients are extra prone to adverse drug reactions. In addition, their management is often challenging given the comorbidities and/or complex organ function impairment [1, 2, 5-8]. Furthermore, polymedicated patients are also at risk of suffering from inappropriate prescribing in the form of underprescription. It has been demonstrated that underprescription increases significantly with the number of medicines used [9]. This situation strengthens the need for routine medication reviews and treatment optimisation [10, 11].

Clinical pharmacist-led medication reviews are considered successful interventions to improve medication safety in the inpatient setting. However, there is limited available evidence of the effects concerning comparable interventions performed in the outpatient setting [1, 12, 13]. In addition, few studies have evaluated health related outcomes resulting from clinical pharmacist interventions in nursing homes. Nevertheless, it has been suggested that most of these studies had major limitations: no control group, no clinical outcome measures, inadequate use of nursing staff to influence change, and data analysis by drug use per provider rather than drug use per patient [6, 8, 10, 11, 13]. Some of these studies were randomised controlled trials performed in the nursing home setting by means of a clinical pharmacists-led medication review; some of them measured the effect of multidisciplinary case conference [6, 26]. In other studies, pharmacists performed the medication reviews and sent suggestions to physicians [8, 10, 15]. Nevertheless, some improvements in patient outcomes have been described [8, 10]. The results from these studies are difficult to compare due to the large differences with respect to the interventions applied, the outcomes studied, the settings, and duration of follow-up after the medication review.

Pharmacotherapy optimisation in nursing home patients relies on the development and assessment of novel healthcare interventions [11]. It is suggested that performing a standardised intervention could potentially lead to a successful medication review; this intervention necessitates pharmacists' and physicians' collaboration, it should include the complete medical and drug history, and fully availability of laboratory values should be guaranteed [10, 12, 13, 17-19].

In the Netherlands, the Dutch Healthcare Inspectorate (IGZ: Inspectie voor de Gezondheidszorg) expects that a medication review is performed by a physician and a pharmacist in all residents of nursing homes yearly; however, this advice implies

substantial extra workload for the involved health care professionals. In addition, in this medication review the information given by the nursing staff and the patient him/herself should also be taken into account.

From our experience, medication reviews involve a time-consuming process that takes an average of 90 minutes per patient. When considering a nursing home of about 150 patients, 450 hours a year would have to be dedicated at performing medications reviews.

In daily practice, this unfortunate situation leads to a non-continuous medication review process implying major consequences that may range from an increased number of potential adverse drug reactions, unnecessary hospitalisations and, at worst, death.

Computerised clinical decision support systems (CCDSS) can be defined as decision-aiding tools which provide health care professionals with clinical knowledge and patient-related information, intelligently filtered or presented at appropriate times, so as to enhance patient care [20-22]. Within the SCREEN project (Supporting Clinical Rules in the Evaluation of Elderly patients with Neuropsychiatric disorders), a CCDSS named Clinical Rule Reporter (CRR) has been developed. This system currently analyses, independently of the applied prescribing software, the medication used by patients in relation to their co-medication, the laboratory data (including renal function), and other relevant clinical data like diagnosis and comorbidities [23]. The CRR combines the clinical rules (algorithms) with the medication list, patient characteristics and laboratory values of the patients in order to obtain concrete advices. These clinical rules or algorithms work with triggers that identify drug related problems like renal or liver dysfunction as well as the need of new medication (stomach protection or laxative agents), the necessity to stop a certain drug or decrease the dose according to age, etc.

Due to the lack of evidence concerning the benefits of medication reviews performed in the nursing home setting, we propose a study aiming to demonstrate a positive effect that the CRR, as a health care intervention, may have on the target population. This population consists of older people (≥65 years) with a high risk of suffering harm when using inappropriate drugs. By this we mean people living in nursing home facilities; these people often suffer from polymedication among other risk factors such as multimorbidity, impaired cognition, renal dysfunction, and increased risk of falling.

The primary objective of this study is to reduce the number of patients with at least one event when using the CRR compared to the regular care. These events consist of hospital referrals, delirium, falls, and/or deaths. Secondary objectives will also be evaluated, including: the analysis within a centre to account for possible differences concerning regular care, the separate analysis for psychogeriatric and somatic

wards, the analysis for medication related events (hospital referrals, delirium, falls, and/or deaths), the separate analysis for each of the parameters included in the combined endpoint, the analysis of the quality of life EQ-5D, the analysis of the MAI (Medication Appropriate Index), and finally, a cost analysis.

Study design

The Supporting Clinical Rules Engine in the Adjustment of Medication (SCREAM) study is a multicentre, prospective, randomised study with a cluster group design. The randomisation will be per main nursing home physician and stratified per ward (somatic and psychogeriatric). This study will be blinded for physicians and for patients; physicians will be emphatically requested not to discuss with each other about the study to avoid bias. The study follows the CONSORT guidelines.

Overall study design

In order to use the CRR, the nursing homes will have to provide the medication list, the patient characteristics and the laboratory values for each patient in a digital format.

Taking into account the extra workload for the investigators, there will be a predefined day for each nursing home to send the files: nursing home A sends the files on Mondays, nursing home B sends the files on Tuesday, and so on.

All nursing homes will send the patient data both for control and intervention groups.

The randomisation will be performed by two of the authors (BvO, CMG). The randomisation will be per main nursing home physician and stratified per ward. Physician A will be randomised in the control group and physician B on the intervention group, taking into account that the number of patients in each group should be approximately the same.

Intervention group: The datasets will be screened through the CRR on a weekly basis. The messages delivered by the CRR will be sent via mail to the specific physicians. Each remark will be sent on a separate mail in a standardised way. In response to the report, the physician will send a feedback message within 36 hours indicating, in a standardised way, whether:

- the advice was not followed
- the advice was followed
- the advice was changed

After receiving this feedback, the investigators will process it in the CRR, in order to create the database for the study.

Additionally, regular care will be also applied. That is according to the Dutch Healthcare Inspectorate, a yearly medication review with a physician and a pharmacist, even though there is a substantial variation [24]. For the centres included in this study there are no dedicated clinical pharmacist working in the nursing home.

Control group: In the control group patients will receive regular care (yearly medication review). In addition, these patients will also be screened using the CRR to obtain data that could serve for future evaluations within the project (for instance to compare how many advices would have been sent from the control group, the difference in remarks, etc.). However, this screening will be performed via a filter and the investigators will neither see nor evaluate any remark. These alerts will only be unblinded at the end of the study.

In addition, for both control and intervention group, the physicians will report any events including: hospital admission, specialist visit, emergency department visit, falls, delirium and death, via a questionnaire. This questionnaire will also include questions to know whether a medication review has been performed and how much time this medication review cost. Physicians will also report if there is any new patient. This electronic questionnair will be sent by Google Drive via email weekly. At the end of the study, the physicians in the intervention group will receive a mail asking how much time, in average, they need to answer the remarks which are sent from the CRR. Figures 1 and 2.

Endpoints

Primary endpoint

The primary outcome variable in this study is the proportion of patients with at least one of the events, including hospital referrals (i.e. referral to a specialist, emergency department visit and hospital admission), delirium, falls, and/or deaths. All these events will be reported by the nursing home physician via the electronic questionnaire. To this end the study will assess the differences between regular care (control group) and regular care + CRR (intervention group).

Secondary endpoints

As secondary endpoints, the same outcome variable will be used to analyse the possible differences between institutions, to separately analyse psychogeriatric and somatic wards, to analyse the medication related events, and to separately analyse each of the parameters included in the combined endpoint (hospital referrals, delirium, falls, and/or deaths).

In order to get this information, physicians will be asked to report any events including: hospital admission, polyclinic visit, emergency department visit, falls, delirium and death. These questions will be asked via an electronic questionnaire via Google Drive. The assessment of whether the event is or could be drug related or not will be done exclusively by the physician.

The quality of life will be measured using the EQ-5D questionnaire both for patients in the control group and patients in the intervention group. The questionnaire will be performed at the end of the study (i.e. after one year follow-up), both for psychogeriatric and somatic patients. The results will be compared between intervention and control group. For both patients groups a caregiver/nurse will answer the questionnaire.

In addition, the analysis of the MAI and the cost evaluation will also be performed for both control and intervention group.

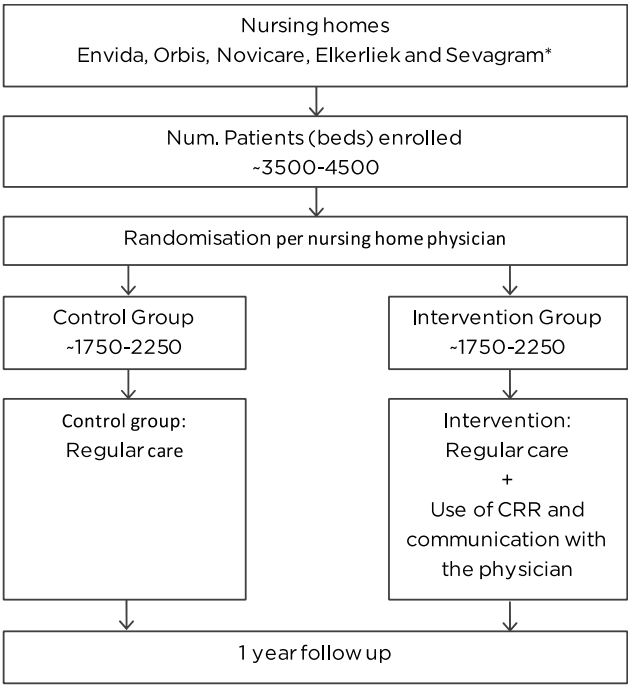

Figure 1. Schematic study design (* other possible centres Amsterdam and Nijmegen)

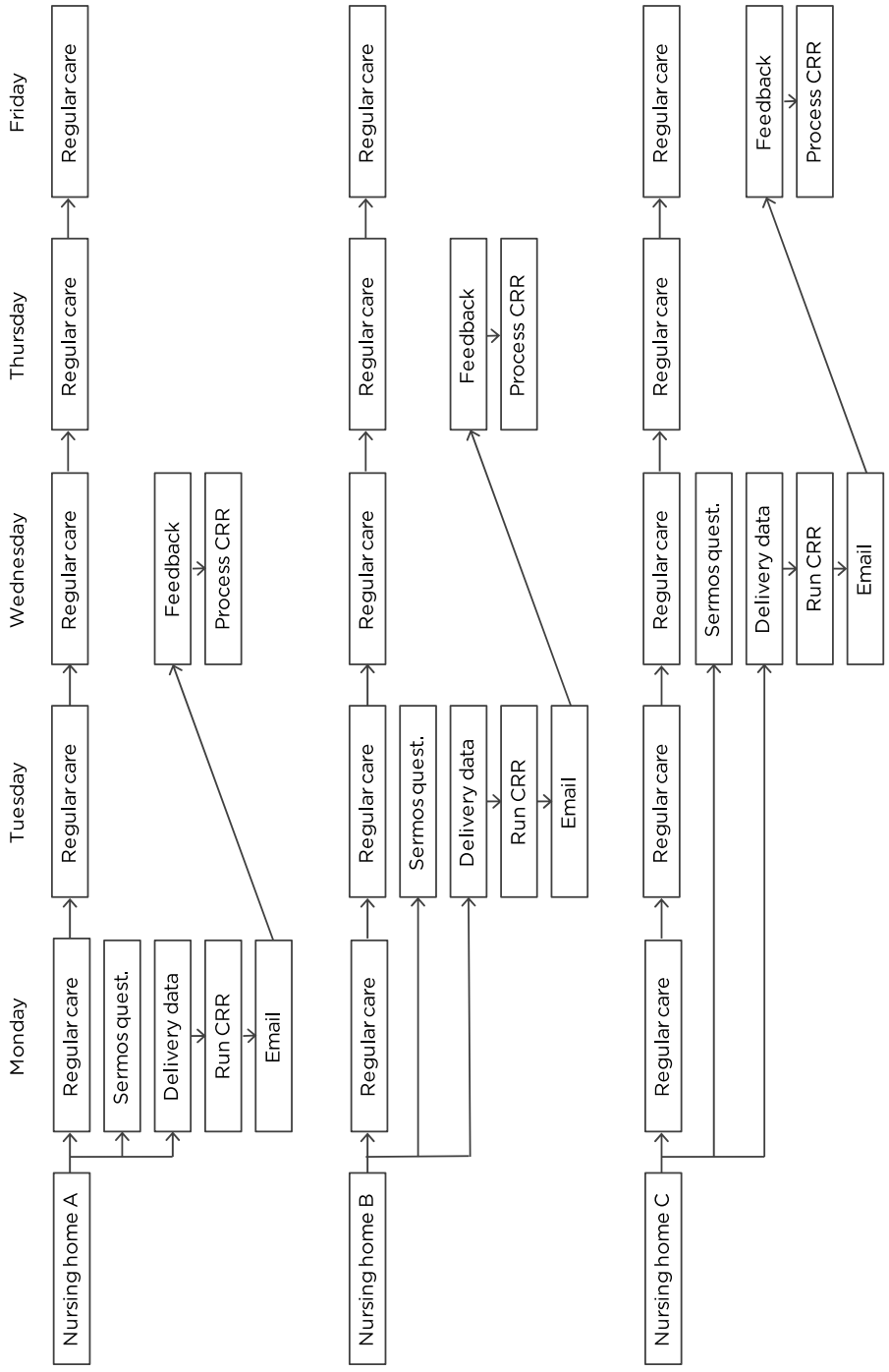

Figure 2. Study schedule

Setting

Nursing homes in the Netherlands will be invited to participate in the study; these nursing homes should be able to deliver the medication data and the laboratory data electronically. In case the data would come from the hospital in the neighbourhood, this hospital would have to agree on providing the data. If a nursing home meets these requirements, it is eligible for participation in the present study.

Population

Nursing home residents; the total study population is estimated to have a total of 3500-4500 patients. This wide range in number of patients comes from the fact that patients will not be included singly but as complete nursing homes. In addition, enough patients should be included to ensure reliable results taking into account possible loss to follow up.

Inclusion criteria

Residents living in a nursing home in the Netherlands.
The nursing homes are able to deliver the medication and lab data electronically.

Participating centres

Zuyderland Medical Centre in Sittard-Geleen (coordinating centre), Envida in Maastricht, Sevagram in Heerlen, Elkerliek in Helmond, and Novicare in different locations. Other centres will be invited and included when the requirements are fulfilled (Amsterdam and Nijmegen).

Randomisation, blinding and treatment allocation

Randomisation: per main nursing home physician. The randomisation will be stratified per ward (somatic and psychogeriatric). In case the physician would be absent the suitable option will be followed:

Absence ≤ 6 weeks intervention group: the mails with the messages obtained from the CRR will still be sent to the main physician. If the replacing physician would also participate in the study, he will not get any mails for the group of patients for which he/she is the replacing physician during this period. It is assumed that if the replacing physician is included in the intervention group, he could apply the mails from his own group to all patients. If the replacing physician is included in the control group, it is assumed that no interventions will be performed.

Absence > 6 weeks intervention group: the mails will be sent to the replacing physician; if the replacing physician would be one of the physicians already included and randomised in the control group, the replacing physician will get the mails only for the patients in the intervention group.

Blinding: Blinded for patients; in addition, physicians will be emphatically requested not to talk about the emails.

Treatment allocation: If a patient dies or moves to another institution, the replacing patient will not take over the place in the study. Death is one of the endpoints for the study and so the study would be completed for that patient; moving to another institution will be considered as loss to follow-up. To account for these patients the physicians will have to report every time a new patient gets in the nursing home, in this way a filter can be applied to not analyse these new patients.

Time schedule

Recruitment started in June 2013; the target population, 3500-4500 patients, is expected to be accomplished in June 2016. The different centres can start with the study at different times. Each centre will be followed for a period of 1 year and afterwards the data analysis will start.

Organisation

Each participating centre has provided a contact person who will be in charge of coordinating the study in their centres. The investigators have regular contact with these coordinating people to confirm the fulfilment of the inclusion criteria, the adherence to the study protocol, and to provide support or additional information when necessary.

Cost analysis

A cost analysis will be performed for both groups (control and intervention).

Hospital costs: The analysis will take into account the number of hospitalisations or hospital referrals, consisting of personnel (physician, nurse, pharmacists, etc.), material and equipment costs. These costs will be based on study patients records and standard rates.

Costs outside the hospital: This analysis will also take into account the healthcare costs outside the hospital like the addition of new medication.

Sample size calculation

Calculation of the total number (one event per patient). The aim is to reduce the number of patients with at least one event with 25% by using the CRR compared to the regular care. These events consist of medication related hospital referrals, delirium, falls, and/or deaths.

In order to calculate the sample, size a pilot study was performed. Nursing homes physicians from the region (Envida and Zuyderland) have informed, via an electronic questionnaire, about any hospital referrals, delirium and/or falls within their patients. In addition, they stated whether these events could be medication related. This pilot study has lasted for 5 months. No patient information was given.

The pilot study showed a proportion of patients with at least one event (combination of fall, delirium, hospital referral, and death) in the control group of 0.16 and a mean number of patients per physician of 56.

Assuming a proportion of patients with at least 1 event during 1 year follow-up of 0.20 in the control group, a 25% reduction by using the CRR compared to regular care, i.e. proportion reduces from 0.20 to 0.15, and a two-sided significance level (α) of 0.05, the number of patients per group required to detect an effect with 80% power equals 906. Accounting for the design effect (randomisation per physician; DE = 1 + (m-1) *ICC), where we assume an intra-class correlation coefficient (ICC) of 0.01, a mean number of patients per physician (m) of 56 (pilot study), and a 10% dropout rate, the required number of patients increases to 1562 per group.

We assumed a higher proportion of patients with at least one event in the control group (0.20) than the one found in the pilot study (0.16), because the number of falls were underreported in the pilot study and the follow-up duration is now longer, i.e. one year instead of five months.

Statistical analysis

To account for the cluster randomisation (physicians are randomised, where patients are clustered within physicians), all linear and logistic mixed effects analyses are performed with physicians as random factor.

Primary study parameters: To detect a difference in proportions of the primary outcome (composite endpoint consisting of hospital referrals, delirium, falls, and/or deaths) between the groups (control versus intervention), logistic mixed effects analysis are applied with the following fixed factors: group (control or intervention), nursing home organisation (Envida, Zuyderland, Sevagram or Novicare), type of ward (psychogeriatric or somatic) and other variables related to the outcome, like age and sex.

Secondary study parameters: For the subgroup analyses (within nursing home organisation or within type of ward), the same analysis method is applied as for the primary outcome variable, excluding the variable that indicates the subgroups.

For the other endpoints, linear or logistic mixed models are used, depending on the type of outcome (numerical or binary, respectively). Furthermore, the same fixed effects as for the primary outcome are included.

Discussion

Other studies have mainly focused on surrogate outcomes as primary endpoint. These endpoints, such as reduction of drugs, MAI or drug costs, fail at showing clinical outcomes [10, 12, 25-29]. In the present study, we are focusing both on hard endpoints (i.e. patient relevant outcomes), and surrogate outcomes. The primary endpoint, however, is a combined set of hard endpoints with a clear clinical outcome. For this reason, the duration of this study is one year; other studies not using hard endpoints have shorter study periods [6, 8, 10, 29]. Furthermore, this study is a multicentre study including over 3000 patients making it a relatively large study in comparison with other studies [6, 8, 10, 27, 28]

A major discussion point with other articles is the fact that a great number of studies focus on reducing the number of prescribed drugs whereas the focus should be on optimising the prescribed drugs (rationalistic pharmacotherapy). This fact enlightens the paradoxically relation between polypharmacy and underprescribing as it might be confronting to add new medication to an already polymedicated patient whereas reducing medication might seem the most logical way to perform [9]. For some patients, optimising the medication will imply reducing the number of drugs, for other patients it will be the changing of some drugs or adding some drugs. [30]

We strongly believe that by using a CCDSS, medication reviews are performed in a standardised way which leads to comparable results between patients. In addition, using a CCDSS eliminates the time factor to perform medication reviews as the major problems related to medication, laboratory values, indications and/or established patient characteristics will be directly available. In this way, and in order to make the medication review process complete, consultation within healthcare professionals and/or the patient itself will be time effective and the medication surveillance could be performed around the clock. Especially for polymedicated patients, like nursing home patients, this system provides a hand full of advantages to provide continuous surveillance, improving in this way patient care.

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Chapter 8

General discussion

Medication reviews

A medication review is defined as a structured evaluation of a patient's medicines with the aim of optimising the medicines' use and improving health outcomes. This entails detecting drug-related problems, recommending interventions and thus preventing the negative effects of drugs and, in a later stage, preventing unplanned hospital admissions related to medication [1]. Polypharmacy can generally be defined as the use of more than a certain number of drugs regardless of their appropriateness [1–3]. In the Netherlands, it has more specifically been defined as the chronic use of five or more drugs from different therapeutic groups or subgroups [4]. In the nursing home population, it is estimated that 1 in every 3 patients is polymedicated [5], and given their considerable frailty, these patients are extra prone to adverse drug reactions. In addition, their management is often challenging given the comorbidities and/or complex organ function impairments [6-11]. When merging these facts, it is only fair to conclude that medication reviews are crucial to maintain a high quality of pharmacotherapy [2, 12-16].

Previous studies have shown that adverse drug events are a common cause for hospitalisations and how medication reviews might have a positive impact on these hospitalisations [2, 17-23]. In the HARM (Hospital Admissions Related to Medication) study, Leendertse et al. found that up to 46% of the drug-related hospital admissions were preventable; based on their findings, they recommended the performance of regular medication reviews in order to improve that outcome [20, 22]. Several initiatives have been pursued to reduce inappropriate medication. The definition of inappropriate medication was first established in the "Beers" criteria for the nursing home population [23,24]. The United States and Canada have explicit criteria for medications considered inappropriate in elderly patients [23,25]. In Europe, the POM (Prescribing Optimisation Method) study focused on 6 questions that should be asked to optimise the prescribing system; the results showed an increase in the proportion of correct decisions when prescribing [26]. Furthermore, the STOPP study established criteria for the detection of potentially inappropriate medication significantly associated with avoidable adverse drug reactions that could cause or contribute to hospitalisation [27]. Conjointly, the START study validated a screening tool to systematically identify appropriately omitted medicines in polypharmacy in older patients [28]. Nevertheless, the quality of medication reviews varies greatly [12, 29]. Several articles have proven the positive effect of medication reviews on polypharmacy; however, its effects on hard endpoints (clinically relevant) remain doubtful [30-33].

In the Netherlands, the Dutch Healthcare Inspectorate (IGZ: Inspectievoor de Gezondheidszorg) requests that a medication review be performed by a physician and a pharmacist for all residents of nursing homes twice yearly; however, this

advice implies a substantial extra workload for the health care professionals involved. In addition, in this medication review, the information given by the nursing staff and the patient him/herself should also be taken into account. From our experience and what we have seen in the literature, medication reviews involve a time-consuming process that takes an average of 90 min per patient. In daily practice, this unfortunate situation leads to a non-continuous medication review process, implying major consequences that may range from an increased number of potential adverse drug reactions, unnecessary hospitalisations and, at worst, death; it can also involve unnecessary costs. In addition, the method in which regular medication reviews are performed might guarantee, at best, structured methods using specific criteria, but they still remain a snapshot of the medication and medical history of a patient [29, 34]. For this reason, and as suggested in the study from Huiskens et al., longitudinal or continuous medication therapy management, targeting specific risk moments, could be a better alternative [34].

Computerised clinical decision support systems

To achieve a longitudinal medication optimisation process, CCDSSs can be used. CCDSSs can be defined as decision-aiding tools that provide health care professionals with clinical knowledge and patient-related information, intelligently filtered or presented at appropriate times, to enhance patient care [35-37].

Using a CCDSSs to support medication reviews implies that reviews are performed in a standardised way, which leads to comparable results between patients. In addition, using a CCDSS eliminates the time factor involved in performing medication reviews, as the major problems related to medication, laboratory values, indications and/or established patient characteristics are directly available. In this way, and in order to make the medication review process complete, consultation within healthcare professionals and/or the patient itself would be more efficient, and the medication therapy management could be performed around the clock.

Furthermore, CCDSSs can target a wide range of actions within the prescribing process, such as treatment monitoring, dose adjustments, and stopping or dwindling therapy, and they can generate lists of patients eligible for a particular intervention by following guidelines or specific protocols [35, 36, 38-44]. Therefore, we strongly believe that a CCDSS, as a healthcare intervention tool, is essential for medication therapy management. This lead to our first question:

Which steps are essential for a transition from a standard medication review process to medication optimisation by means of a CCDSS?

Eberhardt et al. described the development process of a CCDSS [45]. The amount of clinical information and knowledge healthcare professionals have has increased in the last decades thanks to new technologies. This fact can lead to reduced situational awareness and increased mental workload [46]. We propose a CCDSS that supports the medication review process by reducing the time to perform a medication review and generating high-quality suggestions for therapy optimisation. The different phases for the development of the CCDSS are described in Chapter 2. This process involves 5 phases, from the development of the CCDSS as an EPD-independent system, going through the development of the clinical rules and their validation, to finally testing the CCDSS in a randomised control trial and implementing it in other facilities. These phases are based on the "iterative prototyping" of the Systems Development Life Cycle, which are described the iterative process of defining the requirements, designing the system, coding the system, and testing the system, after which the system is implemented. This method is specifically suitable when evolving from a prototype to a working system with a good likelihood of user acceptance [47].

One of the critical steps in the development of the CCDSS is content in the form of clinical rules. It is often said that a CCDSS is as good as the professional behind the algorithms [45, 48, 49]. The first step into the development of the clinical rules lead us to the following question:

Which information is crucial to perform a high-quality medication review, and how might healthcare professionals use such information?

In Chapter 3, different healthcare professionals noted drug indications, medical history, and laboratory values as the most important covariates that would lead to a high-quality medication review. From these observations, it was clear which information should be taken into account when developing the clinical rules. Further into the process, in Chapter 4, healthcare professionals were asked to perform medication reviews by using the covariates that had previously been mentioned as crucial. The clinician's performance was far from ideal, emphasising the large variability on medication review quality. In addition, the study highlighted that information is incorrectly used or wrongly interpreted, regardless of the available information; this matches with the fact that more information can lead to reduced situational awareness and increased mental workload [45, 46].

Clinical rules should follow evidence-based assessments. As validated algorithms, they assign sign- or symptom-based probability scores to risk stratify patients for specific prognoses and/or diagnostic assessments [50-52]. Developing a clinical rule consists of 4 steps: first the problem for which a clinical rule is developed has

to be identified. Second, the algorithm has to be generated, followed by a test phase and finally by implementation [53-55]. Clinical rule development is a highly dynamic process that requires periodic optimisation by re-integrating new knowledge and/or feedback into the development process.

Clinical rules can be classified into 3 groups: knowledge base, expert systems, and predictive algorithms [45].

The first group comprehends clinical rules that present relevant information to the healthcare professional, but the healthcare professional is still responsible for sorting and interpreting such information. This kind of algorithm can be compared with standard medication surveillance, in which an alert is generated for a drug whose dose should be adjusted to renal function without taking into account either the renal function or the dose.

The second group comprehends more sophisticated clinical rules that are focused on a specific problem and are designed to solve it in a specific way. An example of such an expert system algorithm is described in Chapter 5, in which a clinical rule alerting of chronic use of benzodiazepine and a related Z drug is described.

How does the BZ/Z (benzodiazepine and related Z drugs) CR perform in daily practice?

Based on STOPP criteria and SPCs, the clinical rule generated an alert whenever a BZ/Z had been used for more than 4 weeks, advising that it be phased out and eventually stopped. Even though the clinical rule functioned, the decision remained with the physicians who began the process. The success rate was rather low; on the one hand, there were several barriers for actually following the advice, but on the other hand, a less specific clinical rule design could also have played a role.

The third group comprehends predictive algorithms that are mostly aimed at the rapid evaluation of more complex profiles, providing an alert when a patient is at risk of suffering a certain condition, e.g., patients at risk for delirium.

Is it possible to predict delirium in hospitalised patient with a clinical rule?

With high sensitivity and specificity, the DEMO, a fully automated clinical rule to predict delirium in older people, was validated in Chapter 6. The DEMO was developed aiming at predicting delirium 24 hours after analysis. In the validation process, the predictive period was extended, making it possible to predict delirium within 5 days after analysis.

The last phase before the implementation of a CCDSS is its evaluation.

How should a clinical trial for CCDSS be designed?

Liu et al. addressed the fact that, compared to other study areas, clinical trials are not widely applied for medical informatics [56]. In addition, there is a lack of focus on the impact of a CCDSS on clinical outcomes [12, 15, 57-63]. Therefore, in Chapter 7, we present a study design focused on both hard endpoints (i.e., patient relevant outcomes) and surrogate outcomes.

We have studied the current situation of medication optimisation during the medication review process. It seems clear to healthcare professionals in which way medication reviews should be performed and which information should be used to achieve high-quality medication therapy management. Nevertheless, the current situation raises some major issues, one of them being the heterogeneity in which medication reviews are performed, making its quality highly dependent on the healthcare professionals involved; and above all, the fact that current medication reviews are merely a snapshot of a patient's medical and drug history. To perform a more continuous medication optimisation therapy, CCDSSs can be used to objectivise the process by standardising interventions and functioning at a faster rhythm. Using a CCDSS to support the medication review process decreases the time needed to evaluate the appropriateness of medication so that healthcare professionals can focus on what is important and perform a high-quality medication review. When considering the technical possibilities and how sophisticated these systems and algorithms can become, it is only a matter of time before CCDSSs are considered a standard intervention to support the medication optimisation process. From our experience, in order for a CCDSS to be successful, its content must be applicable for a specific setting. In this way, one CCDSS can be a widely applied form for primary to tertiary care, switching certain rules on or off depending on the setting. In addition, enough time should be invested in optimising the clinical rules and finding the balance between evidence-based medicine and feedback from the clinical practice. A clinical rule will only work at its best when the primary objectives of standardising and making the medication optimisation process more efficient are fulfilled. The overall goal from the medication optimisation viewpoint is to improve patient care; thus, the use of a CCDSS should be evaluated on clinical outcomes. This should be the subject of future research, of which the first steps already have been undertaken.

A clinical rule is as good as the person developing it
It depends on the available digital information
It is impersonal
It lacks patient input

BUT

A rules engine does not get tired
It never gets bored
It does not get distracted
It never misses anything
It documents everything it does
It offers no opinions
It is consistent
It does not forget, and always follows up
It frees up time to focus on the true task of a professional, evaluation and decision making

WHAT NOW?

Let's standardise the use of CCDSS
Let's focus on the clinical rules content
Let's make it is as good as technically possible
Let's digitalise all the information
Let's involve the patient
Let's use our freed time to evaluate, discuss and decide
Let's go!

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Summary

Introduction

Polypharmacy and medication review

Polypharmacy can generally be defined as the use of more than a certain number of drugs, regardless of their appropriateness. Polypharmacy increases the risk of adverse effects, often causes problems with patient compliance, and increases the likelihood of inappropriate prescription. Simultaneously, polypharmacy may cause suboptimal treatment because the probability of underprescription paradoxically increases with the number of drugs used.

In the nursing home population, polypharmacy is highly prevalent: it is estimated that one out of every three patients is polymedicated, and given their considerable frailty, these patients are extra prone to adverse drug reactions. In addition, management of comorbidities and/or complex organ function impairment is often challenging. In the nursing home population, a prevalence as high as 40% is found for receiving potentially inappropriate medication. Furthermore, in a recent study it was established that 5.6% of the unplanned hospital admissions in the Netherlands were medication related, and it has been suggested that half of these hospital admissions could have been prevented. This highlights the importance of medication reviews. Medication reviews are the structured evaluation of a patient‘s medicines, with the aim of optimising medicines use and improving health outcomes. This entails detecting drug related problems and recommending interventions, and thus aiming at preventing unplanned hospital admissions related to medication.

In the Netherlands, the Dutch Healthcare Inspectorate requires that at least one medication review is performed yearly by a physician together with a pharmacist for all residents of nursing homes; this is an important and sensible measure to assure the quality of prescribing regimes. However, following this requirement implies a substantial extra workload for the healthcare professionals involved. In addition, in this medication review, the information given by the nursing staff and the patient him/herself should also be taken into account. Different healthcare professionals debate the feasibility of systematic medication reviews. Medication reviews are a time-consuming process, and in daily practice, this unfortunate situation leads to a non-continuous medication review process, implying major consequences that may range from an increased number of potential adverse drug reactions and/or drug related problems, unnecessary hospitalisations and, at worst, death. In addition, standard medication reviews are performed as a cross-sectional intervention at an arbitrary moment during a patient’s drug therapy. It is expected that a longitudinal or continuous medication therapy management, targeting specific risk moments, could be a better alternative.

Computerised Clinical Decision Support Systems (CCDSSs) and Clinical Rules (CRs)

Developing and assessing new care interventions are keys to optimising pharmacotherapy and thus limiting the negative effects of polypharmacy. A CCDSS can be defined as a decision-aiding tool that provides health care professionals with clinical knowledge and patient-related information, intelligently filtered or presented at appropriate times, to enhance patient care. The development of CCDSSs has become an ongoing process of sophisticated generating systems that link patient characteristics with computerised knowledge bases, using algorithms and generating patient-specific assessments or treatment recommendations. CCDSSs and clinical rules are conceived to support a range of clinical daily tasks by integrating the electronic medical record systems and the computerised physician order entry systems in such a way that reminders or warnings can be sent to guide both drug and dosage selection processes and identify deviating laboratory test results, adverse drug reactions, allergies, possible interactions and duplicates. Furthermore, CCDSS and CRs can target a wide range of actions within the prescribing process, such as treatment monitoring, dose adjustments, and stopping or dwindling therapy, and they can generate lists of patients eligible for a particular intervention by following guidelines or specific protocols.

The first step in the transition towards a longitudinal medication therapy management is described in **Chapter 2**, where the development of a CCDSS is presented that, independent of the prescribing software, continuously monitors all prescribed drugs while taking into account co-medication, laboratory-data and co-morbidities.

In order to develop the CCDSS, the covariates that may lead to a high-quality medication review were established in **Chapter 3**. Different healthcare professionals, including community pharmacists, hospital pharmacists, nursing home physicians, general practitioners and geriatricians were asked to rank the relative importance of thirteen covariates. These covariates had been previously established by a research panel selected for their expertise in the field of medication reviews. The most relevant covariates that may lead to a high-quality medication review are: drug's indication, use of patients' medical history, use of guidelines, reviewer's professional field, and use of laboratory values.

Subsequently, these variables were used in **Chapter 4** to evaluate to what extent they are used when performing medication reviews for nursing home patients. A group of 46 healthcare professionals from different fields were requested to perform medication reviews for three different cases. Per case, the amount of information provided varied in three subsequent stages: stage 1) medication list only; stage 2) adding laboratory data and reason for hospital admission, stage 3) adding medical history/drug indication. The remarks from the participants were scored,

compared to the reference reviews, according to their potential clinical impact from relevant to harmful. The overall mean percentage over all cases, stages and groups was 37.0% compared to the reference reviews. The low performance of medication reviews found in the present study highlights that information is incorrectly used or wrongly interpreted, irrespective of the available information. Performing medication reviews without using the available information in an optimal way can have potential implications towards patients' safety.

The next step into the development of the CCDSS was conceiving the clinical rules. Clinical rules are algorithms which combine patient related information and generate patient-specific assessments or treatment recommendations. One of these clinical rules aimed at benzodiazepine and Z related drugs (BZ/Z) use optimisation is presented in **Chapter 5**. A clinical rule was developed to promote the discontinuation of chronically used BZ/Z for insomnia, as the chronic use of BZ/Z in older people is common and not without risks. The clinical rule generated an alert in case of chronic BZ/Z; afterwards the indication insomnia was established. In that case, advices to phase out and eventually stop the BZ/Z were sent to the physician. In total 808 nursing home patients were screened. In 161 of the patients, BZ/Z use resulted in a clinical rule alert. The advice to phase out and stop the BZ/Z was adopted for 27 patients. Even though the success rate for discontinuance of chronically used BZ/Z described in the present study was rather low, a simple clinical rule, which screens all nursing home patients within 5 minutes, can be used to identify which patients qualify for discontinuation.

Another type of clinical rules are predictive algorithms that are mostly aimed at the rapid evaluation of more complex profiles, providing an alert when a patient is at risk of suffering a certain condition, e.g. patients at risk for delirium. A delirium or acute confused state is a transient attention and cognition disorder that develops over a short period of time and occurs mainly in hospitalised patients and people aged 60 years and over. Delirium is an under-diagnosed, severe, costly and often preventable disorder. A fully automated CR to predict delirium (DEMO) in older people was developed, and in **Chapter 6**, the predictive value of the DEMO was validated in the clinical setting. A total of 383 patients were included in this study. The analysis was performed for delirium within 1, 3 and 5 days after a DEMO score was obtained. Sensitivity ranged from 87.1% to 82.7% for 1, 3, and 5 days, respectively, after obtaining the DEMO score. Specificity ranged from 77.9% to 84.5 for 1, 3, and 5 days, respectively, after obtaining the DEMO score. DEMO is a satisfactory prediction model which predicts delirium within 5 days after the analysis.

Finally, the CCDSS and its content should be tested. Therefore, in **Chapter 7**, we present the study design to demonstrate a positive effect that a CCDSS, used to support medication reviews, may have on the nursing home population. This study is a multicentre, prospective, randomised study with a cluster group design. The

primary objective of this study is to reduce the number of patients with at least one event when using the CCDSS compared to the regular care. These events consist of hospital referrals, delirium, falls, and/or deaths. We strongly believe that by using a clinical decision support system, medication reviews are performed in a standardised way which leads to comparable results between patients, eliminating the inter-variability factor. In addition, using a CCDSS also eliminates the time factor to perform medication reviews as the major problems related to medication, laboratory values, indications and/or established patient characteristics will be directly available. In this way, and in order to make the medication review process complete, consultation within healthcare professionals and/or the patient itself will be time effective and the medication optimisation could be performed around the clock.

Conclusion

We have studied the current situation of medication optimisation during the medication review process. It seems clear to healthcare professionals in which way medication reviews should be performed and which information should be used to achieve high-quality medication therapy management. Nevertheless, the current situation raises some major issues, one of them being the heterogeneity in which medication reviews are performed, making its quality highly dependent on the healthcare professionals involved; and above all, the fact that current medication reviews are merely a snapshot of a patient's medical and drug history. To perform a more continuous medication optimisation therapy, CCDSSs can be used to objectivise the process by standardising interventions and functioning at a faster rhythm. Using a CCDSS to support the medication review process decreases the time needed to evaluate the appropriateness of medication so that healthcare professionals can focus on what is important and perform a high-quality medication review. When considering the technical possibilities and how sophisticated these systems and algorithms can become, it is only a matter of time before CCDSSs are considered a standard intervention to support the medication optimisation process. From our experience, in order for a CCDSS to be successful, its content must be applicable for a specific setting. In this way, one CCDSS can be a widely applied form for primary to tertiary care, switching certain rules on or off depending on the setting. In addition, enough time should be invested in optimising the clinical rules and finding the balance between evidence-based medicine and feedback from the clinical practice. A clinical rule will only work at its best when the primary objectives of standardising and making the medication optimisation process more efficient are fulfilled. The overall goal from the medication optimisation viewpoint is to improve patient care; thus, the use of a CCDSS should be evaluated on clinical outcomes. This should be the subject of future research, of which the first steps already have been undertaken.

Samenvatting

Introductie

Polyfarmacie en medicatiebeoordeling

Polyfarmacie kan in het algemeen worden gedefinieerd als het gebruik van meer dan een bepaald aantal geneesmiddelen, ongeacht hun geschiktheid. Polyfarmacie verhoogt het risico op bijwerkingen, veroorzaakt vaak problemen met de therapietrouw van de patiënt en verhoogt de kans op onjuist of incorrect voorschrijven van geneesmiddelen. Tegelijkertijd kan polyfarmacie een suboptimale behandeling veroorzaken, omdat de kans op onderbehandeling paradoxaal genoeg toeneemt met het aantal gebruikte geneesmiddelen.

In de verpleeghuizen komt polyfarmacie veelvuldig voor: naar schatting is één op de drie patiënten een polyfarmacie patiënt en gezien hun fragiliteit zijn juist deze patiënten extra vatbaar voor het optreden van bijwerkingen. Bovendien is het beheer van co-morbiditeit en/of complexe orgaanfunctiestoornissen vaak een uitdaging bij deze patiënten. In de verpleeghuispopulatie wordt een prevalentie van 40% gevonden voor het mogelijk krijgen van ongeschikte medicatie. Bovendien werd in een recente studie vastgesteld dat 5,6% van de ongeplande ziekenhuisopnames in Nederland verband houden met medicatie en is gesuggereerd dat de helft van deze ziekenhuisopnames voorkomen had kunnen worden. Dit benadrukt het belang van medicatiereviews. Een medicatiebeoordeling of medicatiereview is een gestructureerde evaluatie van de medicatie van een patiënt, met als doel het gebruik van medicatie te optimaliseren en de gezondheid te verbeteren. Dit houdt in het opsporen van medicatiegerelateerde problemen en het aanbevelen van interventies, om daarmee ongeplande ziekenhuisopnames met betrekking tot medicatie te voorkomen.

In Nederland eist de Inspectie voor de Gezondheidszorg (IGZ) dat er ten minste één medicatiebeoordeling jaarlijks door een arts samen met een apotheker wordt uitgevoerd voor alle bewoners van verpleeghuizen; dit is een belangrijke en essentiële maatregel om de kwaliteit van voorschrijven en therapie te verzekeren. Het opvolgen van deze eis betekent echter een aanzienlijke extra werklast voor de betrokken beroepsbeoefenaren in de gezondheidszorg. Bovendien moet bij het uitvoeren van de medicatiebeoordeling ook rekening worden gehouden met de informatie die het verplegend personeel en de patiënt zelf hebben verstrekt. Verschillende zorgprofessionals discussiëren over de haalbaarheid van het uitvoeren van systematische medicatiebeoordelingen. Medicatiebeoordelingen zijn een tijdrovend proces en in de dagelijkse praktijk leidt deze situatie tot een niet-continu medicatiecontrole proces, wat grote consequenties met zich meebrengt die kunnen variëren van een verhoogd aantal potentiële bijwerkingen van geneesmiddelen en/of medicatiegerelateerde problemen, onnodige ziekenhuisopnames en in het

slechtste geval de dood. Daarnaast worden standaard medicatiereviews uitgevoerd als een cross-sectionele interventie op een willekeurig moment tijdens de behandeling van een patiënt. Het is te verwachten dat een longitudinaal of continu medicatietherapie beheer, gericht op specifieke risicomomenten, een beter alternatief kan zijn.

Computerised Clinical Decision Support Systems (CCDSSs) en Clinical Rules (CRs)

Het ontwikkelen en beoordelen van nieuwe zorginterventies is de sleutel tot het optimaliseren van de farmacotherapie en daarmee het beperken van de negatieve effecten van polyfarmacie. Een CCDSS kan worden gedefinieerd als een beslissingshulpmiddel dat zorgprofessionals voorziet van klinische kennis en patiëntgerelateerde informatie, die op een intelligente wijze wordt gefilterd of op gepaste tijden wordt gepresenteerd, om zo de patiëntenzorg te verbeteren. De ontwikkeling van CCDSSs is een doorlopend proces geworden van geavanceerde systemen die kenmerken van patiënten koppelen aan geïnformatiseerde databanken, en die door het gebruik van algoritmen patiëntspecifieke beoordelingen of aanbevelingen voor de behandelaar genereren. CCDSSs en CRs (klinische beslisregels) zijn ontworpen om een reeks dagelijkse klinische taken te ondersteunen door een EVS (Elektronisch Voorschrijf Systeem) en EPD (Elektronisch Patiënten Dossier) zodanig te integreren dat herinneringen of waarschuwingen worden verzonden om zowel geneesmiddel- als doseringsprocessen te begeleiden en afwijkende laboratoriumresultaten, bijwerkingen, allergieën, mogelijke interacties en dubbelmedicatie te identificeren. Bovendien kunnen CCDSSs en CRs zich richten op een breed scala aan acties binnen het voorschrijfproces, zoals behandelingsmonitoring, dosisaanpassingen en stop- of afbouwende therapie, en kunnen ze overzichten genereren van patiënten die in aanmerking komen voor een specifieke interventie door het volgen van richtlijnen of specifieke protocollen.

De eerste stap in de overgang naar een longitudinaal medicatie optimalisatie wordt beschreven in **Hoofdstuk 2**, waar de ontwikkeling van een CCDSS wordt gepresenteerd die, onafhankelijk van EVS en/of EPD, alle voorgeschreven geneesmiddelen continu bewaakt, rekening houdend met comedicatie, laboratoriumuitslagen en comorbiditeit.

Om het CCDSS te ontwikkelen, zijn variabelen die kunnen leiden tot een hoogwaardige medicatiebeoordeling vastgesteld in **Hoofdstuk 3**. Verschillende professionals in de gezondheidszorg, waaronder openbaar apothekers, ziekenhuisapothekers, verpleeghuisartsen, huisartsen en geriaters werden gevraagd om het relatieve belang van dertien variabelen aan te geven. Deze variabelen waren eerder vastgesteld door een onderzoeksteam dat geselecteerd was op basis van hun expertise op het

gebied van medicatiebeoordelingen. De meest relevante variabelen die kunnen leiden tot een hoogwaardige medicatiebeoordeling zijn: indicatie van het geneesmiddel, gebruik van de medische (voor)geschiedenis van de patiënt, gebruik van richtlijnen, professioneel vakgebied van de beoordelaar en gebruik van laboratoriumuitslagen.

Vervolgens zijn deze variabelen in **Hoofdstuk 4** gebruikt om te evalueren in hoeverre deze worden gebruikt bij het uitvoeren van medicatiebeoordelingen voor verpleeghuispatiënten. Een groep van 46 professionals in de gezondheidszorg uit verschillende vakgebieden werd gevraagd om medicatiebeoordelingen uit te voeren voor drie verschillende casussen. Per casus varieerde de hoeveelheid verstrekte informatie in drie opeenvolgende fasen: fase 1: alleen beschikking over de medicatie lijst; fase 2: toevoegen van laboratoriumuitslagen en reden voor ziekenhuisopname; fase 3: toevoegen van medische voorgeschiedenis/geneesmiddelindicatie.

De opmerkingen van de deelnemers werden gescoord in vergelijking met de referentiebeoordelingen, op basis van hun mogelijke klinische gevolgen van relevant tot schadelijk. Het algemeen gemiddelde percentage over alle casussen, fasen en groepen was 37,0% in vergelijking met de referentiebeoordelingen. De lage prestatie van medicatiebeoordelingen in dit onderzoek tonen aan dat informatie onjuist wordt gebruikt of verkeerd geïnterpreteerd wordt, ongeacht de beschikbare informatie. Het uitvoeren van medicatiebeoordelingen zonder de beschikbare informatie optimaal te gebruiken, kan mogelijke gevolgen hebben voor de veiligheid van de patiënt en de kwaliteit van leven.

De volgende stap in de ontwikkeling van de CCDSS was het ontwerpen van de clinical rules. Clinical rules zijn algoritmen die patiënt gerelateerde informatie combineren en patiënt specifieke beoordelingen of aanbevelingen voor de behandeling genereren. Een van deze klinische regels richt zich op benzodiazepine en benzodiazepine agonisten geneesmiddelen (BZ/Z) gebruiksoptimalisatie en wordt gepresenteerd in **Hoofdstuk 5**. Er is een CR ontwikkeld om het stoppen van chronisch gebruikte BZ/Z voor slapeloosheid te bevorderen, gezien het chronisch gebruik van BZ/Z bij ouderen niet zonder risico's is. De CR zorgde voor een waarschuwing in geval van chronisch gebruik van BZ/Z; achteraf werd op basis van EPD en gebruik de indicatie slapeloosheid vastgesteld. In dat geval werden adviezen om de BZ/Z geleidelijk af te bouwen en uiteindelijk te stoppen naar de voorschrijver gestuurd. In totaal werden 808 verpleeghuispatiënten gescreend. Bij 161 van de patienten resulteerde BZ/Z-gebruik in een clinical rule waarschuwing. Het advies om de BZ/Z geleidelijk af te bouwen en te stoppen werd opgevolgd voor 27 patiënten. Hoewel het succespercentage voor stoppen van chronisch gebruikt BZ/Z beschreven in de huidige studie vrij laag was, kan een eenvoudige CR, die alle verpleeghuispatiënten binnen 5 minuten screened, worden gebruikt om patiënten die in aanmerking komen om te stoppen met BZ/Z te identificeren.

Een ander soort clinical rules zijn voorspellende algoritmen die gericht zijn op de snelle evaluatie van meer complexe profielen, waarbij een waarschuwing wordt gegeven wanneer een patiënt het risico loopt aan een bepaalde aandoening te krijgen, b.v. patiënten met een risico op delier. Een delier of acute verwarde toestand is een voorbijgaande aandachts- en cognitiestoornis die zich in korte tijd ontwikkelt en voornamelijk voorkomt bij gehospitaliseerde patiënten en mensen van 60 jaar en ouder. Delier is een ondergediagnosticeerde, ernstige, kostbare en vaak te voorkomen aandoening. Een volledig geautomatiseerde CR om delier bij ouderen te voorspellen (DElirium MOdel DEMO) werd ontwikkeld en in **Hoofdstuk 6** is de voorspellende waarde van DEMO gevalideerd in de klinische setting. Een totaal van 383 patiënten werd geïncludeerd in deze studie. De analyse werd uitgevoerd voor het optreden van een delier binnen 1, 3 en 5 dagen nadat een DEMO-score was verkregen. De sensitiviteit varieerde van 87,1% tot 82,7% voor respectievelijk 1, 3 en 5 dagen na het behalen van de DEMO-score. De specificiteit varieerde van 77,9% tot 84,5 voor respectievelijk 1, 3 en 5 dagen na het behalen van de DEMO-score. DEMO is een effectief voorspellingsmodel dat delirium binnen 5 dagen na de analyse voorspelt. Ten slotte moeten de CCDSS en de inhoud ervan worden getest. Daarom presenteren we in **Hoofdstuk 7** het studieontwerp om een positief effect aan te tonen dat een CCDSS, gebruikt om medicatiebeoordelingen te ondersteunen, mogelijk heeft op de verpleeghuispopulatie. Deze studie is een multicenter, prospectief, gerandomiseerd onderzoek met een clusterontwerp. Het primaire doel van deze studie is om het aantal patiënten met ten minste één incident bij gebruik van de CCDSS te verminderen in vergelijking met de reguliere zorg. Deze incidenten bestaan uit doorverwijzingen door het ziekenhuis, het optreden van delier, vallen en/of sterfgevallen. We zijn ervan overtuigd dat medicatiebeoordelingen die met behulp van een CCDSS op een gestandaardiseerde wijze worden uitgevoerd, leiden tot vergelijkbare resultaten tussen patiënten, en dus elimineert de intervariabiliteit factor. Bovendien elimineert het gebruik van een CCDSS ook de factor tijd om medicatiebeoordelingen uit te voeren, omdat de belangrijkste problemen met betrekking tot medicatie, laboratoriumuitslagen, indicaties en/of vastgestelde patiëntkenmerken direct beschikbaar zijn. Op deze manier, en om het medicatiebeoordelingsproces te voltooien, is overleg tussen zorgverleners en/of de patiënt zelf tijdeffectief en kan de medicatie-optimalisatie 24 uur per dag worden uitgevoerd.

Conclusie

We hebben de huidige situatie van medicatieoptimalisatie bestudeerd binnen het medicatiebeoordelingsproces. Het lijkt voor professionals in de gezondheidszorg duidelijk op welke manier medicatiereviews moeten worden uitgevoerd en welke

informatie moet worden gebruikt om een hoogwaardig beheer van medicatietherapie te bereiken. Niettemin brengt de huidige situatie enkele belangrijke problemen met zich mee, waaronder de heterogeniteit waarmee medicatiebeoordelingen worden uitgevoerd, waardoor de kwaliteit ervan sterk afhankelijk is van de betrokken professionals in de gezondheidszorg; en vooral, het feit dat de huidige medicatiebeoordelingen slechts een momentopname zijn van de medische en medicatiegeschiedenis van een patiënt. Om een meer continue medicatie-optimalisatietherapie uit te voeren, kunnen CCDSSs worden gebruikt om het proces te objectiveren door interventies te standaardiseren en op een snellere manier te laten functioneren. Het gebruik van een CCDSS om het medicatiebeoordelingsproces te ondersteunen, vermindert de tijd die nodig is om de medicatie te evalueren, zodat zorgprofessionals zich kunnen richten op wat belangrijk is en een hoogwaardige medicatiebeoordeling kunnen uitvoeren. Wanneer we kijken naar de technische mogelijkheden en hoe verfijnd deze systemen en algoritmen kunnen zijn, is het slechts een kwestie van tijd voordat CCDSS als een standaardinterventie worden beschouwd om het medicatieoptimalisatieproces te ondersteunen. Onze ervaring is dat een CCDSS alleen succesvol kan zijn als de inhoud ervan van toepassing is op een specifieke instelling of patiënt. Op deze manier kan één CCDSS een veel toegepaste vorm zijn voor primaire tot tertiaire zorg, waarbij bepaalde regels afhankelijk van de instelling worden in- of uitgeschakeld. Daarnaast moet voldoende tijd worden geïnvesteerd in het optimaliseren van de clinical rules en het vinden van de balans tussen evidence-based medicine en feedback uit de klinische praktijk. Een CR werkt het beste als de primaire doelstellingen om het medicatieoptimalisatieproces te standaardiseren en efficienter te maken worden vervuld. Het algemene doel vanuit het oogpunt van medicatieoptimalisatie is het verbeteren van de patiëntenzorg; dus, het gebruik van een CCDSS moet worden beoordeeld op klinische uitkomsten. Dit zou het onderwerp moeten zijn van toekomstig onderzoek, waarvan de eerste stappen reeds zijn ondernomen.

Valorisation

Polypharmacy is defined as the simultaneous use of more than a certain number of drugs, regardless of their appropriateness [1]. Polypharmacy increases as people get older and it is estimated that 20% of patients 65 of older is polymedicated [2]. Previous studies have shown that polypharmacy increases the risk of drug related problems (DRPs) and can lead to hospitalisation [3].

Medication optimisation aims at improving health outcomes by optimising the use of medication, taking into account the benefits and safety aspects of the used drugs; It consists of medication surveillance and medication reviews. Medication surveillance is daily (digitally) performed by physicians and/or pharmacists to assure a beneficial and safe use of drugs and combinations of multiple drugs. It alerts for drug-drug interactions, drug-disease interactions (contraindications) and incorrect dosages. Medication reviews are structured evaluations of a patient's medicines, patient's characteristics, and laboratory values performed periodically (manually) aiming at optimal pharmacotherapy. Medication optimisation, the combination of medication surveillance and medication reviews, is thus aimed at detecting DRPs so that interventions can be recommended to prevent unplanned hospital admissions [1].

The fact that medication reviews are performed, at its best, periodically, emphasizes that this traditional way might be out of date, as it is a snapshot of a patient's medication list, characteristics and laboratory results [4, 5].

A transition towards a more up to date method is essential to guarantee a high-quality medication optimization process, hopefully showing in clinically relevant outcomes. In this way, a computerised decision support system (CCDSS) seems a plausible answer. These systems were created in the 70's to support the clinician on making diagnosis and treatment decisions. CCDSS are typically designed to integrate a medical knowledge base, patient data and an inference engine to generate case specific advice [6].

This thesis puts in perspective the methodological aspects of the medication optimization process and discusses new strategies in the form of CCDSS.

We have shown that even when having all the available information which could lead to a high-quality medication review, its quality leaves much to be desired

Different healthcare professionals (community pharmacists, hospital pharmacists, nursing home physicians, general practitioners and geriatricians) ranked the importance of different covariates in order to perform a high-quality medication review. From this survey, we could establish that drug's indication, use of patients' medical history, use of guidelines, reviewer's professional field, and use of laboratory values are the top 5 covariates that would lead to a high-quality medication

review. Subsequently, these covariates were used to perform medication reviews and we demonstrated the large variability on their quality.

The Dutch healthcare inspectorate (IGZ) demands a medication review to be performed twice a year and yearly for all nursing homes residents and elderly home residents, respectively. Taking into account the time required to perform a medication review, the disappointing quality of the medication reviews performed and the lack of proven efficacy, it is surprising that the healthcare inspectorate requires the medication reviews to be performed. A multidisciplinary working group is adapting the guidelines which patient should be reviewed in order to make it more feasible for general practitioners and pharmacists. They suggest an increase of both the age and the number of drugs used, thereby discarding the view that early detection of DRP's leads to prevention and minimising damage.
Given these facts and taking into account the time needed to perform a medication review, a more efficient way is needed to fulfil the expectations. Furthermore, a longitudinal or continuous medication therapy management would be a better approach than a cross-sectional approach to assure optimal pharmacotherapy.

This thesis shows which aspects should be considered to optimise the efficiency when performing medication review supported by a CCDSS

Using a CCDSS to perform medication reviews might lead to a significant time reduction increasing the process efficiency.

The content of a CCDSS is known as clinical rules which are the algorithms generating patient-specific assessments or treatment recommendations. Clinical rules assign sign- or symptom-based probability scores to risk stratify patients for specific prognoses and/or diagnostic assessments.

Optimising the clinical rules is the first step towards a high-quality medication optimisation. In this way alerts are generated only when action is required. For example, an alert is generated according to renal function value and drug dose. In the basic medication surveillance, an alert is generated for each drug whose dose should be adjusted to the renal function without taking into account either the renal function or the dose. In order to prevent alert fatigue on one hand, but also missing important alerts on the other hand, we aim at a clinical efficacy of 80%. We realise however that this 80% is not evidence based. This might be a topic for future research.

Simple clinical rules can be used to identify patients eligible for treatment optimisation, making the screening process more efficient and objective

Clinical rules can also be used to select a group of patients eligible for a specific treatment based on beforehand established parameters. Within this project a clini-

cal rule to promote the discontinuation of chronically used BZ/Z for insomnia in the nursing home setting was developed.

Even though the discontinuation rate was rather low, we have shown that a simple clinical rule can screen more than 800 patients and generate a list within minutes of the patients which according to guidelines are qualify for discontinuation. In addition, when using a clinical rule no patient is missed and the same criteria is objectively applied to screen all patients. This approach makes it possible to run this clinical rule more frequently, e.g. on a weekly basis.

We have validated an automated delirium prediction model which by means of a clinical rule can predict patients at risk of delirium within 5 days after analysis

Delirium is an under-diagnosed, severe, and costly disorder, and 30-40% of cases can be prevented [7]. A fully automated model to predict delirium (DEMO) in older people was developed and has been validated in this thesis.

Patients admitted in the hospital are automatically screened within 24 hours from admission. DEMO predicts patients at risk of developing a delirium within 5 days after analysis. The high sensitivity and specificity found in the validation study make the model satisfactory to be applied in clinical practice to facilitate earlier recognition and diagnosis of delirium. Nevertheless, important factors that could predict delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model as these data are not yet electronically available.

Using a CCDSS will drastically reduce the time to perform a medication review and hopefully demonstrate a positive effect on clinically relevant outcomes compared to traditional medication review

Clinical trials are not widely applied for medical informatics. In addition, there is a lack of focus on the impact of a CCDSS on clinical outcomes. We present a RCT study design focused on both hard endpoints (i.e., patient relevant outcomes) and surrogate out-comes, aiming at demonstrating a positive effect on clinically relevant outcomes when using a CCDSS vs traditional medication optimisation in the nursing home setting.

The overall goal from the medication optimisation viewpoint is to improve patient care; thus, the use of a CCDSS should be evaluated on clinical outcomes. This should be the subject of future re-search, of which the first steps already have been undertaken.

In addition, using a CCDSS to support the medication review process decreases the time needed to evaluate the appropriateness of medication so that healthcare professionals can focus on what is important and perform a high-quality medication review.

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Ik had nooit gedacht dat ik überhaupt en eigen thesis zou hebben…

Ik had nooit gedacht dat ik …

maar dan is het zover…

het laatste stukje…

misschien wel het lastigste, al hoeft het niet gepubliceerd te worden!

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Beste SCREEN-team:

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Beste Bob, hi! Je bent een van de enige die mijn flowchart frustraties kan begrijpen! Moet het LT of LTEQ zijn? GT of GTEQ? De meeste zullen weten wat een DDD is, maar jij weet dan ook wat de FDD, PDD en vooral de WDD zijn! Bedankt voor alle ondersteuning tijdens het maken van de clinical rules!

Beste collegae:

Beste Piet, Rob, Hugo (boss), Dennis, Niels, Kobra, Brigit, Hugo (young). Jullie zijn mijn Sittardse familie (nu nog altijd!), ook al zitten jullie niet meer allemaal daar. Het is ook niet niks wat ik met jullie heb meegemaakt! Van stage naar promotie traject en dan in combinatie met de opleiding tot ziekenhuisapotheker. Thanx voor alles

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Hugo (young), jou laatste jaar en mijn eerste! Op dat moment wist ik niet dat we allebei onze opleiding delirant zouden gaan afronden! Jij bent er ook altijd voor mij geweest. Irritaties, frustraties, en the happy moments tijdens dit onderzoek hebben we samen gedeeld en uiteraard gevierd! Heel veel succes met je nieuw baan collega HiXer!

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Lieve paranimfen en partynimfen,

Lang geleden in een café in het mooie Barcelona, met een glaasje wijn (of twee…) dacht ik daar zijn ze! Mijn toekomstige paranimfen… het heeft even geduurd, maar…

Lieve, lieve B, in jou heb ik de beste collega gehad, ik moet steeds denken aan onze CR-sessies, de never ending K rule, brainstormsessies etc… Maar wat nog belangrijker is, jij bent, als vriendin, een van de grootste pilaren van mijn leven. Super bedankt voor je steun tijdens mijn opleiding en onderzoek! Super bedankt voor onze ontbijt sessies, onze dubbel dates (inmiddels trippel!). Ik kijk uit naar alles wat nog gaat komen!

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Dear family,

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My love, without you I wouldn't be here today... Literally!!! I can't not even begin to describe what you mean to me. You understand, respect and support me. You make things easier when it gets hard. You are my better half. I can't wait to continue building our future together, every tomorrow starts with you and I wouldn't want it any other way! LYTIAB

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- C -

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Curriculum vitae

Carlota Mestres Gonzalvo was born on the 1st of June 1986 in Barcelona, Spain. In 2004 she finished high school at Fundació Collserola in Barcelona; that same year she started her pharmacy degree at University of Barcelona. During the university years she worked in different community pharmacies in Spain and followed a summer internship in a community pharmacy in the Netherlands (Apotheek Born) were she met her husband. Half way 2010 Carlota moved to the Netherlands and started her last internship for the study doing research on the oncology field at the Clinical Pharmacy, Pharmacology and Toxicology department at Orbis Medical Center in Sittard.

After obtaining her Master's Degree in 2011 she started research within the SCREEN project (Supporting Clinical Rules in the Evaluation of Elderly patients with Neuropsychiatric disorders), which would later lead to her PhD research. In 2013 she started the hospital pharmacist specialization at Orbis Medical Center under supervision of dr. PHM van der Kuy. Carlota combined her specialization with her PhD project within SCREEN.

Carlota finished her specialization in April 2017 and has since been working as a hospital pharmacist at Elkerliek hospital. She's is continuing her research as a postdoc working on CHECkUP.

Let’s standardise the use of CCDSS

Let’s focus on the clinical rules content

Let’s make it is as good as technically possible

Let’s digitalise all the information

Let’s involve the patient

Let’s use our freed time to evaluate, discuss and decide

Let’s go!