Appropriate psychotropic drug use in institutionalized people with dementia.
The PROPER-study

Klaas van der Spek

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COLOFON

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CONTENTS

CHAPTER 1
GENERAL INTRODUCTION

BACKGROUND

In 2015 there was an estimated 46.8 million people worldwide living with dementia. This number will almost double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050. Although much research focusses on the treatment, yet there is neither cure nor treatment that considerably slows or stops its progression. In the meantime, the average age of people is increasing worldwide and there are estimates of 9.9 million new cases every year [1].

Dementia is a syndrome that results in cognitive decline, functional decline and often also neuropsychiatric symptoms (NPS). Different (manifestations of) NPS are described in dementia, e.g. agitation, aggression, anxiety, apathy, delusions, depressive symptoms, hallucinations, sleeplessness, wandering, and are also referred to as behavioral and psychological symptoms in dementia (BPSD) [2]. NPS have been identified as an integral part of the disease from the earliest descriptions of dementia, described by Alois Alzheimer in the beginning of the 20th Century [3] [4]. Some research attributes NPS to neurotransmitter [5][6][7][8] or neuropathological changes [9] whereas others describe its etiology more on personality and psychosocial factors [10] [2]. In this context the last few years, the biopsychosocial model is used, that hypothesizes that the (extent of) the NPS is not only explained by the disease itself but also by the physical and psychosocial environment of the patients [11]. The prevalence of NPS, associated with dementia is estimated at 72%-80% [12][13]. NPS are associated with poor quality of life [14][15] of patients with dementia and burden for the caregiver [16].

In the Netherlands approximately 270.000 people have dementia, 150.000 do not have a proper diagnosis, 52.000 of these cases are known by general practitioners and 70.000 patients reside in Dutch long-term care facilities. However, these figures are estimates based on dated research [17][18][19]. Nursing home care differs between countries [20]. The Netherlands is the only country in the world with specialized Elderly Care Physicians (ECP's)[21][22]. Among other types of care for the elderly, e.g. geriatric rehabilitation or palliative care, ECP's provide dementia care to people that reside on Dementia Special Care Units (DSCUs). Most of the institutionalized patients with dementia reside on DSCUs [23][24]. On these units, care is provided by multidisciplinary teams consisting of ECP's, pharmacists, psychologists and nurses, all of whom are employed by the nursing home. DSCUs are specialized in treating patients in Global Deterioration Stages 4 - 7 of dementia and unit sizes vary from 5 to 30 patients, with typically 1 nurse per 5-6 residents. Usually patients have one nurse assigned as primary responsible caregiver, that is also involved in reporting NPS in patients and discussing the patients'(medical) treatment [25].

Psychosocial interventions are the first choice of management for NPS [26][27][28], however, NPS are frequently a reason for prescription of psychotropic drugs (PDs) [25][29][30], i.e. antipsychotics, anxiolytics, hypnotics, antidepressants, anticonvulsants, and anti-dementia drugs. PD use rates in institutionalized patients with dementia vary from 63%-75% [12][31][30].

PDs have considerable side effects. Antipsychotics are associated with increased occurrence of extrapyramidal symptoms, somnolence, increased risk for stroke and pneumonia and higher mortality rates [32][33][34], although controversy exists of the latter[35][36][37]. Anxiolytic and hypnotic drugs are associated with falls [38]. PDs in general [14] and antipsychotics in particular also have negative effects on quality of life [15]. It is also known that antipsychotic use varies among countries between 11% and 54% [30][39][40][41][42][43].

Guidelines emphasize the restricted, short-term use [28]. However, long-term inappropriate use of PDs is common [44]; a recent study found that 31% of the nursing home patients used PDs for a sustained period (≥2 years) [31] and in another study 74 % of dementia patients in nursing homes used PDs for 83% of their nursing home stay [45]. Many studies report that PDs are used too long [46] [44][31], with sometimes duplicate prescription [47][48], and without a proper indication [49][50]. This does not comply with available evidence on risks, side effects, limited evidence for efficacy of these drugs and long-term inefficacy [34][51].

In sum, there are many challenges physicians face in treating dementia patients for NPS appropriately. Moreover, there is an ever increasing interest in reducing PD use in nursing homes internationally [52][53]. However, with the initiatives to reduce the frequency of (inappropriate) PD use, there seem to be little attention for prescriptions that have appropriate indications and appear to be effective when evaluated. While that could be key for beneficial PD use, consequently improving its effectiveness and reducing inappropriate use. Potentially, intervening on the appropriateness instead of just reducing these prescriptions could lead to improved NPS treatment.

APPROPRIATENESS OF PSYCHOTROPIC DRUG USE
Many different definitions have been established to describe the appropriateness of drug prescriptions, that include indications [54], regularly evaluating the prescriptions [55], the administration and pharmaceutical aspects like dosage, drug-drug interaction, drug-disease interaction and therapy duration [56][57]. For many of these (individual) aspects there exist evidence based guidelines for PD use that formulated recommendations.

Aspects that relate to the broader concept of appropriateness, that integrates guideline adherence, have previously not been studied.

AIM OF THIS THESIS

PDs are prescribe too long and inappropriately for NPS, however, we do not exactly know what appropriate PD prescription in dementia is. Therefore, the first aim of this thesis is to investigate the appropriateness of PD prescriptions and its associations; a research index needs to be developed that is specialised in measuring all relevant indicators of the appropriateness of PDs for NPS in dementia.

Using this index the current status of the appropriateness of these prescriptions can be calculated and factors associated to more or less appropriateness can be explored.

The second aim of this thesis is to execute an intervention to improve the appropriateness of these prescriptions and measure its effect with the newly developed index.

RESEARCH QUESTIONS AND GENERAL OUTLINE

How to measure appropriateness of psychotropic drug prescriptions?

Although there are different assessment instruments to objectify (potentially) inappropriate prescriptions, e.g. Beers criteria [58], Medication Appropriateness Index [59] and START and STOPP [60], none of these are specifically suited to measure the appropriateness of PD prescriptions for NPS in patients with dementia. Therefore a measure especially suited for this purpose needs to be developed.

Chapter 3 gives an overview of the development of an instrument that is suited for measuring appropriateness of PD prescriptions for NPS in patients with dementia in nursing homes, and to test its reliability and validity.

How appropriate are psychotropic drug prescriptions for neuropsychiatric symptoms?

Chapter 4 concerns the assessment of the appropriateness of PD prescription for NPS in nursing home patients with dementia. The study design is described in **chapter 2**. Current status of the appropriateness of PD prescription for NPS in nursing home patients with dementia is explored, and more specifically the domains of appropriateness of PD prescription for NPS that contributed the most to appropriate use are investigated. Potential differences between PD types in the appropriateness of use and association between the appropriateness of PD prescription and the number of PDs used (frequency of use) per patient, DSCU, and elderly care physician are studied.

What factors are associated with the appropriateness of psychotropic drug prescriptions?

Although several studies [11][61][62][63][64][65] investigated factors associated with the frequency of PD use, we only found one study that reports about factors associated with the appropriateness of PD prescriptions in dementia; it was found that presence of behavioral symptoms and female sex were associated with more appropriate indications of benzodiazepines [54].

Chapter 5 describes research on the appropriateness of PD prescription for NPS in nursing home patients with dementia and its associations, i.e. related to patients, physicians and nurses. The study design is also described in **chapter 2.**

How to improve the appropriateness of PD prescriptions?

The Dutch Healthcare Inspectorate advises to use national guidelines in the prescription of PDs and to biannually evaluate the effect of these prescriptions and if ineffective stop these prescriptions.

Both systematic reviews [66][67] as well as individual studies [66][60][68] in different settings, i.e. hospital [66][60] and nursing homes [68], show that a multidisciplinary medication review with the involvement of a pharmacist [67] and the additional presence of a nurse [67] has beneficial effects on appropriate drug prescription. Although there is evidence to suggest that a medication review may result in the improved appropriateness of drug prescription in general [69][68], studies on psychotropic drug prescription in dementia are lacking thus far.

This trial, the PROPER-II study, of which the design was described in **chapter 6** and the outcomes in **chapter 7**, concerns the effect of a structured multidisciplinary medication review supported by education on the appropriateness of PD prescription for the treatment of NPS in nursing home patients with dementia.

Finally in **chapter 8** the main findings of this thesis are summarised and discussed.

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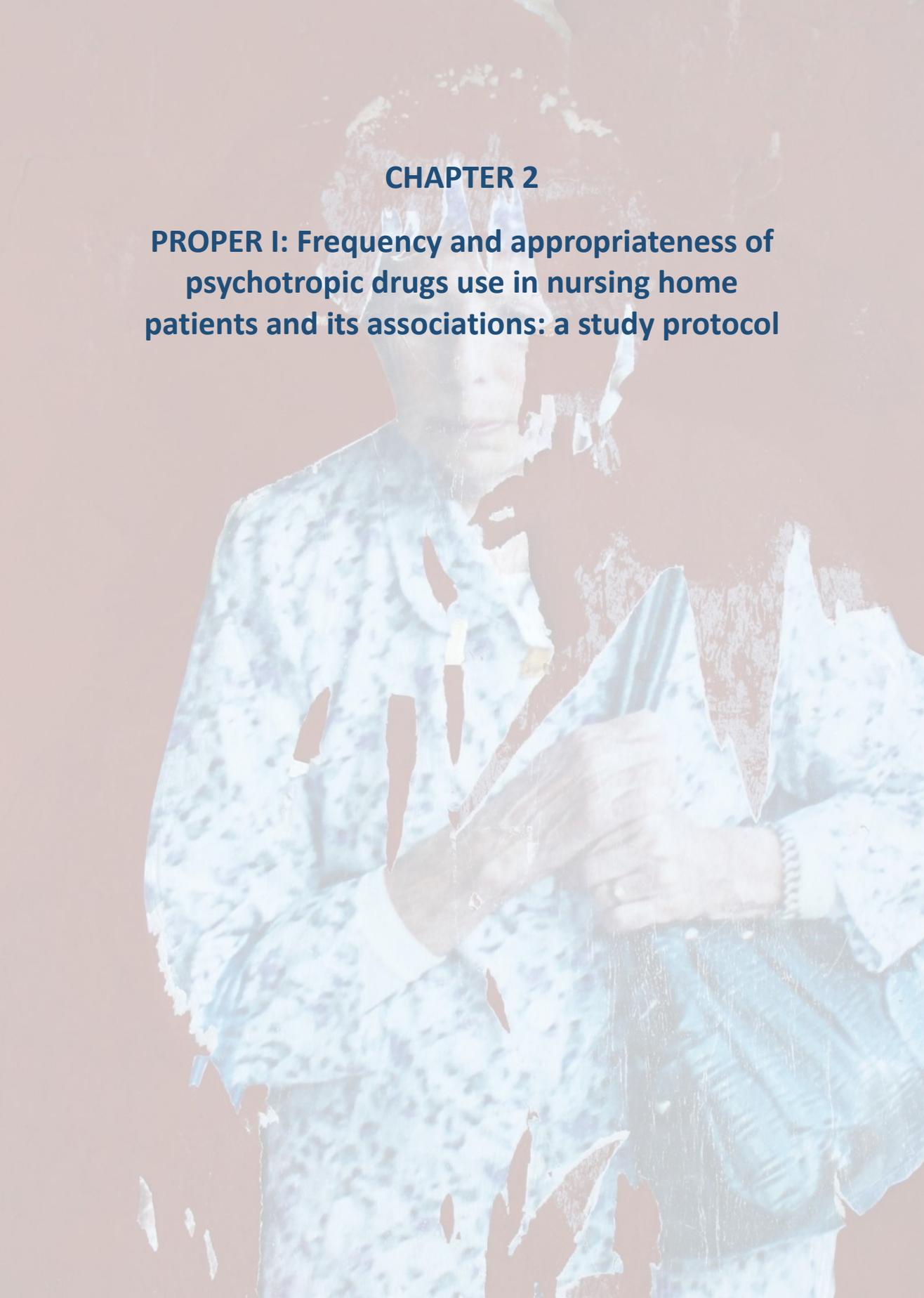
CHAPTER 2

PROPER I: Frequency and appropriateness of psychotropic drugs use in nursing home patients and its associations: a study protocol

CHAPTER 2

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ABSTRACT

Background

Nursing home patients with dementia use psychotropic drugs longer and more frequently than recommended by guidelines implying psychotropic drugs are not always prescribed appropriately. These drugs can have many side effects and effectiveness is limited. Psychotropic drug use between nursing home units varies and is not solely related to the severity of neuropsychiatric symptoms. There is growing evidence indicating that psychotropic drug use is associated with environmental factors, suggesting that the prescription of psychotropic drugs is not only related to (objective) patient factors. However, other factors related to the patient, elderly care physician, nurse and the physical environment are only partially identified. Using a mixed method of qualitative and quantitative research, this study aims to understand the nature of psychotropic drug use and its underlying factors by identifying: 1) frequency and appropriateness of psychotropic drug use for neuropsychiatric symptoms in nursing home patients with dementia, 2) factors associated with (appropriateness of) psychotropic drug use.

Methods

A cross-sectional mixed methods study. For the quantitative study, patients with dementia (n=540), nursing staff and elderly care physicians of 36 Dementia Special Care Units of 12 nursing homes throughout the Netherlands will be recruited. Six nursing homes with high average rates and six with low average rates of psychotropic drug use, based on a national survey about frequency of psychotropic drug use on units, will be included. Psychotropic drugs include antipsychotics, anxiolytics, hypnotics, antidepressants, anticonvulsants and anti-dementia drugs. Appropriateness will be measured by an instrument based on the Medication Appropriateness Index and current guidelines for treatment of neuropsychiatric symptoms. Factor associated to psychotropic drug use, related to the patient, elderly care physician, nurse and physical environment, will be explored using multilevel regression analyses. For the qualitative study, in depth interviews with staff will be held and analyzed to identify and explore other unknown factors.

Discussion

This study will provide insight into factors that are associated with the frequency and appropriateness of psychotropic drug use for neuropsychiatric symptoms. Understanding psychotropic drug use and its associations may contribute to better dementia care.

Keywords

Nursing home, dementia, neuropsychiatric symptoms, psychotropic drug use, environment.

BACKGROUND

In the Netherlands approximately 37.000 patients with dementia reside in Dementia Special Care Units (DSCUs) of nursing homes [1][2]. The prevalence of neuropsychiatric symptoms (NPS) associated with dementia is high, more than 80% [3], and frequently a reason for prescription of psychotropic drugs (PDs) [4][5][6]. However, psychosocial interventions and restraints are also commonly used in the management of NPS [7]. Psychotropic drug use (PDU) rates in institutionalized patients with dementia vary from 63%-75% [8][9][6]. It is also known that antipsychotic use varies among countries between 11% and 52% [6][10][11][12].

PDs have considerable side effects. Antipsychotics are associated with increased occurrence of extrapyramidal symptoms, somnolence, increased risk for stroke and pneumonia and higher mortality rates [13][14][15]. Anxiolytic and hypnotic drugs are associated with falls [16]. PDs in general [17] and antipsychotics in particular also have negative effects on quality of life [18].

Long-term or inappropriate use of antipsychotics is common [19], a recent study found that 31% of the nursing home patients used PDs for a sustained period of at least 2 years [9] and in another study 74% of dementia patients in nursing homes used PDs for 83% of their nursing home stay [20]. This does not comply with available evidence on risks, side effects, limited evidence for efficacy of these drugs and long-term inefficacy [15][21][22]. That is why guidelines emphasize the restricted, short-term use and thus the appropriateness of PDU [23].

PDU varies considerably among nursing homes and DSCUs [24] [25]. This could partly be explained by different prevalence rates of NPS among patients on DSCUs [3]. However there is growing evidence that this inter-DSCU variation in PDU is not only related to the severity of patients' NPS [6][26]. The PDU variation is also related to drug prescription policies of the Elderly Care Physician (ECP) [5], staff distress/workload [26], physical environmental factors [25], and the bed capacity of the nursing home [27](see figure 1).

Although studies [26][27] investigated frequency of PDU and its associated environmental factors a large proportion, 80%, of the variation in PDU between DSCUs is unexplained [25]. The unexplained variation of PDU, the long-term use and the inter-DSCU variation raise questions not only about appropriateness of prescription, but also about factors associated with the variation in frequency and appropriateness of PDU. That is why we propose a conceptual framework of PDU and four categories of factors with which PDU is hypothesized to be associated: patient, ECP, nurse and physical environment. More specifically, possible other associations related to PDU are: 1. patients' demographic characteristics and influence of psychosocial

environment (relatives and other patients) 2. physicians' demographic characteristics and attitude to dementia care 3. nurses' job satisfaction, experienced organizational culture, demographic characteristics and attitude to dementia care 4. the physical environment, e.g. nursing home characteristics and DSCU characteristics.

Depicted in the conceptual framework we hypothesize that PDU frequency and appropriateness are associated with these four categories of factors, the use of psychosocial interventions and restraints are seen as alternatives to PDU in the framework (see figure 1). To obtain full insight in (possible) associations mixed methods of quantitative and qualitative research will be used.

We aim to study: 1. the frequency and appropriateness of PDU for NPS in nursing home patients with dementia 2. factors associated with frequency and appropriateness of PDU related to patient, ECP, nurse and physical environment.

Figure 1. A conceptual framework on psychotropic drug use in nursing homes and its associations.
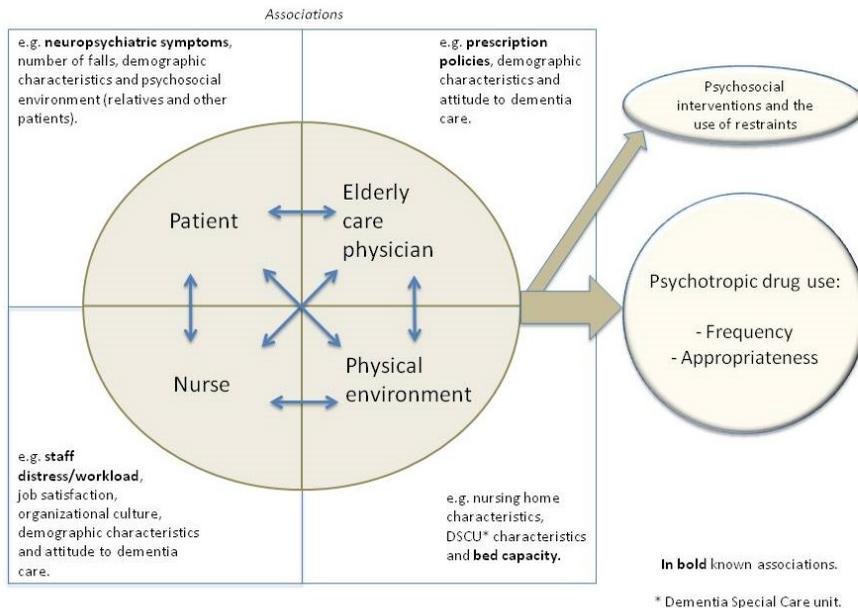
METHODS/ STUDY DESIGN
Design and eligibility
This study, the PROPER I study (PRescription Optimization of Psychotropic drugs in Elderly nuRsing home patients with dementia) is a cross-sectional mixed methods study and will be followed by the PROPER II study (Smeets et al., submitted), a multi-center cluster randomized controlled, pragmatic trial on the efficacy of structured repeated multidisciplinary review on psychotropic drugs. The eligibility of nursing homes is based on a survey among ECPs working in nursing homes that we will carry out among all members of Verenso, the Dutch association of ECPs and community geriatricians. ECPs will be asked to count the number of patients, living on the DSCU they are responsible for, that receive one or more PDs. Nursing homes will be eligible if their ECPs fill in the survey about PDU for at least 3 DSCUs.

Study population and recruitment
According to our calculations (see section on sample size), 36 DSCUs need to be recruited. Based on the results of the survey, 36 DSCUs will be divided over six nursing homes with high and six with low DSCU overall PDU rates. DSCUs with medium rates will be accepted if the nursing home's overall rate is high or low on average; at least two out of three DSCUs need to score high or low within a nursing home. With this selection method the contrast in PDU among nursing homes is increased, which could facilitate finding relevant parameters of PDU, without loss of statistical dispersion for our analyses. No geographical considerations will be made in the recruitment process.

Measurements
The following instruments will be used to explore frequency and appropriateness of PDU and its associations, i.e. patient, ECP, nurse and physical environment related associations. Associations will be explored by quantitative and qualitative measures.

Quantitative measures
Frequency and appropriateness of PDU, primary outcome
PDU will be classified using the Anatomical Therapeutical Chemical (ATC) classification [28] and grouped into antipsychotics, anxiolytics, hypnotics, antidepressants, anticonvulsants and anti-dementia drugs.

For determining appropriateness of psychotropic drug use a screening tool will be developed, based on the Medication Appropriateness Index (MAI). The MAI was developed in 1992 [29] to determine the drug's appropriateness for individual patients on 10 items and is proven to be reliable [30] and applicable

in the Dutch nursing home setting [31]. However, the MAI is not specifically developed as a tool to screen medical files for appropriateness of prescription of individual psychotropic drugs in dementia and thus does not sufficiently suit the needs for this study. We will therefore adapt the original MAI and develop an instrument that screens medical files for appropriateness of psychotropic drug prescription in dementia. The instrument will primarily screen PDs based on the Dutch association of ECP and community geriatricians (Verenso) guideline for problem behavior [23]. The instrument will also include information about interactions and contraindications that originates from the database of the Royal Dutch Association for the advancement of Pharmacy (KNMP) [32]. PD information that is not provided by the Dutch Verenso guideline, will be derived from 'Farmacotherapeutisch Kompas' [33], published by the Dutch Health Care Insurance Board (CVZ) and based on the summary of product characteristics (SPC)[34]. Items will be weighted by an expert panel of pharmacists and ECPs who categorize the relative contribution of each item to the level of drug appropriateness.

Patient factors
NPS will be assessed with the validated Dutch version of the 12-item Neuropsychiatric Inventory- Questionnaire (NPI-Q) [35] [36]. The NPI-Q assesses NPS in dementia and caregiver distress. The NPI-Q measures the occurrence and severity of NPS on a three-point Likert scale and associated caregiver burden on a five-point Likert scale.

Additionally, frequency of agitation and aggression will be assessed with the Cohen-Mansfield Aggression Inventory (CMAI) [37], of which the original and the translated Dutch version has been proven reliable and valid [38][39]. The CMAI consists of 29 individual items, each rated at a seven-point Likert scale, combined to 3 subscales of (physically) aggressive, physically non-aggressive and verbally agitated behavior [38].

Information about other patient characteristics that will be derived from patients' charts are: duration of institutionalization, dementia-type, number of falls, demographic characteristics (date of birth, sex), the use of activities, the use of psychosocial interventions (reality orientation training, reminiscence, validation, aromatherapy, music therapy, light therapy, psychoeducation, sensory activation/snoezelen, multisensory stimulation, cognitive stimulation and psychomotor therapy) and restraints (use of side rails, using a deep chair for patients, use of table stand or chair at table, forced or camouflaged administration of sedative medication, fixing patients with tools (tires, span sheets, tear suits, wristbands, swedish bands), seclude in room with/without the door locked, forced administration of fluid or food and use of electronic alerts).

ECP factors

'Attitude to dementia care' will be measured by Approaches to Dementia Questionnaire (ADQ) [40]. The ADQ consists of 19 items, on a five-point Likert scale and measures hopefulness and person-centredness of professionals in dementia care. Higher scores indicate positive attitudes. The total score ranges from 19-95, the 8-item sub score 'Hope' from 8-40, and the 11-item sub score 'Person-centeredness' from 11-55. Information about demographic characteristics of the physician/ECP will be collected: age, sex, years of work experience, number of years since education/specialization.

Nurse factors

Experienced organizational culture will be measured with the Competing Values Framework Scale (CVFS)[41], the validated Dutch version [42], a 6-item scale where four phrases need to be set in an order of personal relevance. The CVFS assesses the 6 dimensions of the competing values framework [43] : dominant organizational characteristic, administration, management style, organizational glue, strategic emphasis and criteria for success.

Workload will be assessed with a workload questionnaire 'werkdruklijst' developed by De Jonge [44][45]. This scale consist of 10 items about unit workload, each item can be scored on a five-point Likert scale.

Situations, feelings and thoughts about dementia care will also be administered, with a 29-item scale, which will be published as the Strain in dementia Care (SDC) scale (Michael Bird and Anna-Karin Edberg, personal communication 2013). There's a four-point Likert scale for each item, also a score on another four-point Likert scale can be given for professional caregiver burden related to the item. Higher scores indicate high workload.

Job satisfaction will be measured with the Maastricht Work Satisfaction Scale for Healthcare (MAS-GZ) [46][47]; a 21-item, five-point Likert scale that focuses on nursing staff satisfaction. It consist of seven subscales with three items each about satisfaction with: quality of care, opportunities of self-actualization/growth, supervisor, possibilities for promotion, clarity of tasks and rules, contact with colleagues and contact with patients. 'Attitude to dementia care' will be measured by the ADQ (see physician level) [40].

Information about demographic characteristics of the nurse will be collected: age, sex, educational level, work experience, number of years since education.

Factors of the physical environment

Physical environmental characteristics of the DSCU will be assessed using the Therapeutic Environment Screening Survey for Nursing Homes (TESS-NH)[48]. The TESS-NH contains 84 discrete items plus an open global scale that covers 13 domains, i.e. number of patients on unit, exit control, maintenance, cleanliness, safety, orientation/cueing, privacy, unit autonomy, outdoor access, lighting, noise, visual/tactile stimulation, space/seating and familiarity/home likeliness [48].

Other information about DSCU characteristics that will be collected are: number of staff per unit, number of staff during different shifts.

Qualitative interviews, ECP and nurse level

The ECP and 1-2 members of nursing staff will be interviewed about PDU. The qualitative interviews will be semi-structured and based on the Straussian grounded theory approach [49][50]. Interviews will be guided by a checklist of the following (relevant) topics: influence of psychosocial environment (relatives and other patients), PD prescription in practice, own beliefs, beliefs of colleagues, beliefs of patient's family, PDU now and in the past, influence of the institution, best solutions for NPS, education, politics and media.

Table 1. Mixed methods research parameters/instruments

Quantative	Parameters	Instruments	Registered by
Patient level	Frequency of PDU	ATC classification codes	Researchers
	Appropriateness of PDU	To be announced	Researchers
	Neuropsychiatric symptoms	NPI-Q	Nurse (web based)
	Agitation and aggression	CMAI	Nurse (web based)
	Other patient characteristics	Case report file	Researchers
Physician level	Attitude to dementia care	ADQ	ECP (web based)
	Demographic characteristics	Case report file	ECP (web based)
Nurse level	Organizational culture	CVFS	Nurse (web based)
	Workload/burnout	SDC + Werkdruk (De Jonge)	Nurse (web based)
	Work satisfaction	MAS-GZ	Nurse (web based)
	Attitude to dementia care	ADQ	Nurse (web based)
	Demographic characteristics	Case report file	Nurse (web based)
Physical environmental level	Physical environment	TESS-NH	Researchers
	Other DSCU characteristics	Case report file	Researchers
Qualitative	**Parameters**	**Instruments**	**Registered by**
Attitudes and beliefs	Relevant qualitative factors ECP	Semi structured interview	Researchers
	Relevant qualitative factors nurse	Semi structured interview	Researchers

Psychotropic drug use (PDU), Anatomical Therapeutical Chemical (ATC), Neuropsychiatric Inventory- Questionnaire (NPI-Q), Cohen-Mansfield Aggression Inventory (CMAI), Approaches to Dementia Questionnaire (ADQ), Elderly Care Physician (ECP), Competing Values Framework Scale (CVFS), Strain in dementia Care (SDC), the Maastricht Work Satisfaction Scale for Healthcare 'Maastrichtse Arbeidssatisfactie Schaal voor de Gezondheidszorg' (MAS-GZ), Therapeutic Environment Screening Survey for Nursing Homes (TESS-NH).

Data analysis

Quantitative (descriptive and multivariate) and qualitative analyses will be performed.

For quantitative data analysis a multilevel model is built to investigate the potential associations with the frequency of PDU and with the appropriateness of PDU, taken into account that appropriateness of PDU is nested within DSCUs.

Data collection and analysis of the qualitative semi-structured interviews will be conducted as an iterative process with saturation as a guiding principle[51], implying interviews will be carried out until knowledge saturation is reached. This is known as the constant comparative method, which is part of the grounded theory approach [51].

Sample size

According to the n/10 rule [52][53] 360 patients are sufficient to study the number of variables needed for this study. 67% of the patients are expected to use PDs, which means that in total 540 patients need to be recruited. Regarding good sampling and an average cluster size of 15 patients per DSCU, 36 DSCUs of twelve different nursing homes will be recruited.

Ethical approval

The study is undertaken in accordance with the declaration of Helsinki and will be carried out in accordance with the applicable rules in the Netherlands. According to the Medical Ethics Committee of the region Arnhem-Nijmegen, the Netherlands, the study does not need to be conducted according to the Medical Research Involving Human Subjects Act (WMO), because patients will not be directly involved. Relatives, if not available other representatives, of patients will be informed and asked if they object to the collection of data. If the relatives or representatives object, patients will be excluded from the data collection.

DISCUSSION

The high rates of long-term PDU [9] in combination with the risk of major and hazardous side effects, limited evidence for efficacy, long-term inefficacy [15][21][22] and guidelines recommending to regularly evaluate PDU [23], make it crucial to study PDU appropriateness and its associations.

It is hypothesized that the frequency as well as appropriateness of PDU varies between DSCUs, because of factors related to patient, ECP, nurse and physical environment, as described in a conceptual framework (figure 1). More specifically, it is expected that factors like workload and staff distress influence the appropriateness of PDU.

A strength of this study is that the recruitment focuses on nursing homes/ DSCUs with low versus those with high PDU. Knowledge about extreme, i.e. low or high, PDU and its associations is most important in dementia care.

Although the instrument used for measuring appropriateness of PDU needs to be developed specifically for this study, no other instruments known are suitable to investigate the appropriateness of PDU for NPS. However, it should be taken into account that the instruments' assessment of appropriateness of PDU relies on medical files, which may be subjected to bad reporting. Yet, in our view this procedure is considered to be more objective than personal reports of ECPs.

Many of the instruments used for this study are well known in this field of research, and will contribute to giving clear insight in factors related to PDU, which can be used in improving nursing home patient care.

The mixed design of the study is another strength of this study, interviewing ECPs and nurses can reveal relevant factors that are not measured with quantitative instruments. So, this study not only gives insight into frequency and appropriateness of PDU, but also into a diversity of possible associations, which can be used in future quantitative research. PROPER I will provide insight in associations of (appropriateness of) PDU and thus the barriers of optimal prescription, which is the first step towards safer PDU.

COMPETING INTERESTS
The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS
SZ designed the study, DG and MS co-designed, and RK assisted in designing the study. KS wrote the paper, and DG, MS, MN, RW, CS, SZ, and RK co-wrote the paper. All authors read and approved the manuscript.

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CHAPTER 3

A reliable and valid index was developed to measure appropriate psychotropic drug use in dementia

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ABSTRACT
Objective
The aim of this study is to develop an index derived from the Medication Appropriateness Index (MAI) items that is suited for clinical studies evaluating appropriateness of psychotropic drug use (PDU) for neuropsychiatric symptoms (NPS) in patients with dementia in nursing homes, and to test its reliability and validity.

Study design and setting
An expert panel reviewed the MAI items in order to develop items for appropriateness of PDU; a second, independent, expert panel determined content validity of the items. An inter-rater reliability study was conducted (N=54) and a summated index score, based on weighted item scores, was developed to enhance the use in clinical studies. Construct validity was explored using a representative sample of 560 medical records.

Results
Five existing MAI items were used, the MAI item 'indication' was adjusted, a new item 'evaluation' was added and scoring rules were based on guideline recommendations, to create the Appropriate Psychotropic drugs use In Dementia (APID) index. The second expert panel concluded that all items contributed to the construct 'appropriateness'. All items and the summated index score had moderate to almost perfect inter-rater reliability (ICCagreement 0.577-1). The summated index score showed promising construct validity, e.g. no multicollinearity issues were found.

Conclusion
The results of this study show that the APID index is reliable and valid for measuring appropriateness of PDU for NPS in dementia in nursing homes in clinical studies.

Keywords
Appropriate, psychotropic drug use, dementia.

INTRODUCTION

What is new?

Key findings
- A research index is developed to measure appropriate psychotropic drug use in nursing home patients with dementia, with moderate to almost perfect inter-rater reliability and good construct validity.

What this adds to what was known?
- The newly developed index adds a method for medical file research in measuring appropriateness of psychotropic drug use for neuropsychiatric symptoms in dementia.

What is the implication and what should change now?
- With this instrument we are not only able to look at absolute prescription rates but also to its appropriateness, which helps clinicians to optimize and not just reduce psychotropic drug use.

Psychotropic drugs (PDs) are frequently prescribed in nursing homes [1][2][3][4], in particular for the treatment of neuropsychiatric symptoms (NPS)[3][5], e.g. agitation/aggression, psychosis, depression and apathy [6]. Many different groups of PDs are prescribed for this purpose, i.e. antipsychotics, anxiolytics, hypnotics, antidepressants, anticonvulsants and anti-dementia drugs [7]. Although PDs are frequently prescribed, their efficacy is limited [8][9], especially for the long term [10]. PDs are not only used frequently but also persistently, for a period longer than 3 months [11][12], Given that antipsychotics prescribed for NPS in dementia should only be used for a period of 3 months [13]anxiolytics and hypnotics for a period of 2-4 weeks [13] this indicates that antipsychotics, anxiolytics and hypnotics in particular have inappropriate duration of therapy [7]. Additionally, Finkers et al. found that the majority of the patients in nursing homes have at least one drug prescribed of which the indication was unknown [14]. These findings point at inappropriate use.

Furthermore, adverse drug events [15] and hospitalization have been related to inappropriate prescription [16][17]. Particularly, antipsychotics have been shown to cause adverse events, i.e. extra pyramidal symptoms, somnolence, increased risk of falls, stroke and mortality [18][19][20][21]. Pinpointing at inappropriateness of psychotropic drug use (PDU) may help optimizing it in the future, and may even reduce adverse events.

The retrospective application of 'appropriateness' criteria to assess medication use is referred to as drug utilization reviews [22]. Based on this concept several tools and indexes have been developed for the measurement of inappropriate drug use [23]. One of these has been shown to be reliable [24] and applicable in the nursing home setting [25], the Medication Appropriateness Index (MAI) [26]. However, the MAI is an index to measure appropriateness of drug prescription in general, but it is not specifically developed for assessing appropriateness of PDU for NPS in dementia. Additionally, the MAI does not fit specific drug utilization formularies, which is preferable when drug utilization reviews are applied [27] [28]. Formularies that contain evidence-based international medication recommendations for physicians on when and how to use PDs for patients with dementia and NPS, should be applied.

Hence, to estimate appropriateness of PDU for NPS in dementia, the MAI has to be adjusted [29].

The aim of this study is to develop an index that is suited for measuring appropriateness of PDU for NPS in patients with dementia in nursing homes, and to test its reliability and validity.

METHODS

For the use in clinical research [30], an index to measure appropriateness of PDU, prescribed for NPS in patients with dementia in nursing homes, based on patient medical record inspection [31], was developed. To enhance its use for clinical studies a summated index score was constructed [32]. The development of the index was guided by a formative model [33]. This means that the items, or causal indicators in this case [34], together determine the construct 'appropriateness' instead of reflecting the underlying construct. This also implies that neither Classical Test Theory nor Item Response Theory are applicable [33]. In figure 1, an example is provided from other research. Similar use of these models can be applied in measuring drug use where, for example, drowsiness is a reflective measure for (in)appropriate psychotropic drug use and the correct indication is a formative measure for appropriate drug use.

Index development was performed in the following step-by-step approach using measurement techniques according to the work of Diamantopoulos [35], Streiner and Norman[36], and de Vet [33] : 1) the index construction (see section 2.1); 2) the study of item inter-rater reliability (2.2); 3) the construction of a summated index score (2.3); and 4) the study of construct validity (2.4).
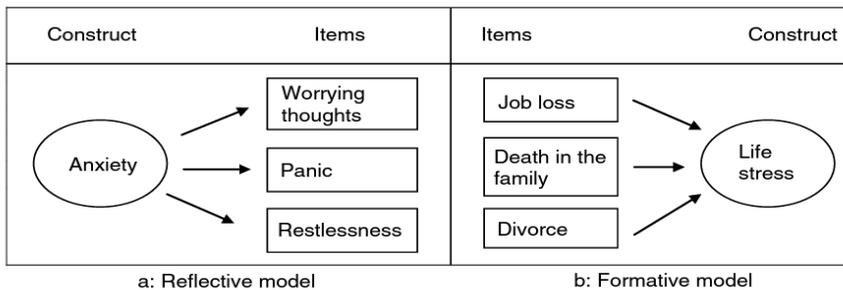
Figure 1. Graphical representation of a reflective (a) and formative model (b).
Source, reprinted with permission: De Vet H, Terwee C, Mokkink L KD.
Measurement in Medicine: A Practical Guide. *Cambridge; 2011.*

For this study we used two expert panels and three samples of nursing home patients with dementia. These will be described in the pertaining sections. All statistical analyses were performed using IBM SPPS Statistics version 20.0.

Index development
An expert panel of one pharmacist and four elderly care physicians (expert panel 1) developed the index by extensively reviewing the literature [30], and thus the constructs' contextual domain [37]. All panel members are also scientists who have extensive knowledge in the field of dementia research. The development was validated by a second independent expert panel (expert panel 2). Expert panel 2 consisted of ten clinical and scientific experts in PDU and NPS in dementia, i.e. three clinical pharmacologists, one pharmacist, two geriatricians/pharmacologists, one psychiatrist and three elderly care physicians.
The index development consisted of two parts; (2.1.1) selection of items for 'appropriateness of PDU for NPS in dementia', (2.1.2) development of scoring rules and instructions for medical record inspection.

Selection of items for 'appropriateness of PDU for NPS in dementia'
To establish which items determine the construct 'appropriateness of PDU for NPS in dementia', expert panel 1 used the MAI items as a basis. The MAI consists of 10 items, i.e. indication, effectiveness, dosage, correctness of directions, practicality of directions, drug-drug interaction, drug-disease interaction, duplication, expense and duration of therapy [31]. The panel members were asked to identify which of these were relevant items and whether new items should be added for the construct 'appropriateness of PDU for NPS in dementia'. Subsequently, expert panel 2 was asked if each of the preselected items was relevant, to determine content validity.

Development of scoring rules and instructions for medical record inspection
The index has to focus on the appropriateness of PDU for NPS in nursing home patients with dementia. Therefore, PDs that had a clear indication for psychiatric disorders in the medical record were excluded from scoring. The expert panel considered sleeping disorder and delirium to be an exception, as these are frequently associated with dementia and are difficult to differentiate from NPS. Therefore, both were also included in the scoring.

This resulted in the following inclusion criteria: a) PDs prescribed for NPS, b) PDs prescribed for sleeping disorder in dementia, c) PDs prescribed for delirium in dementia, based on the indication found in the medical record, d) when an indication for the PD was not found in the medical record, it was assumed that the PD was prescribed for NPS.

First, three ordinal response categories were constructed: appropriate, marginally appropriate and inappropriate, scoring 0, 1 and 2 respectively. This scoring structure makes it possible to add multiple PDs prescribed for one patient. Hence, a patient' overall appropriateness score can be given.

Second, expert panel 1 constructed scoring rules for these response categories, to unify the interpretation by different raters. The scoring rules were primarily based on the Verenso guideline for problem behavior (VGPB) [7]. This guideline, based on evidence from international research, includes recommendations for medical treatment of NPS in dementia.

Additionally, the scoring rules included information about drug-drug interactions and drug-disease interactions that originates from the database of the Royal Dutch Association for the advancement of Pharmacy (KNMP) [38]. Information about indication, dosage and duration of therapy of specific PDs that was not provided by the VGPB guideline, was derived from the 'Farmacotherapeutisch Kompas' [39]. Both the KNMP and the 'Farmacotherapeutisch Kompas' are databases that derive their information from the summary of product characteristics (SmPC)[13]. The Medication Evaluation Board published the SmPC. Henceforth, these databases will be referred to as the SmPC.

Drugs were grouped using the Anatomical Therapeutic Chemical classification (ATC) [40], on ATC3 level, into antipsychotics (N05A) anxiolytics (N05B), hypnotics (N05C), antidepressants (N06A), anticonvulsants (N03A) and anti-dementia drugs (N06D) [3].

The appropriateness of PDU was assessed for the used PDs per patient on the day of medical record inspection. Information was obtained from the patient's medical records and pharmacist files. Expert panel 1 determined the medical record inspection periods per item and per drug group. These periods are the

dates in the medical record where the physician could have written down relevant information needed for the rater to score the item.

Prior to data collection the scoring rules and instructions for medical record inspection were pilot tested twice, by three researchers, to test if the index was applicable and to adjust the medical record inspection periods where needed. In both pilot tests, the medical records of ten nursing home patients were rated.

Item inter-rater reliability

To study inter-rater reliability of the items, two independent raters assessed a random sample of 54 medical records and pharmacist files (sample 1), drawn from the PROPER-study I [30] sample. All subjects from the sample were patients residing in Dementia Special Care Units (DSCUs).

Firstly, the inter-rater reliability analysis focused on absolute agreement and chance-adjusted agreement. Secondly, two sources of (dis)agreement between raters were addressed: the application of scoring rules and the selection of relevant text from the medical record.

To obtain more insight into the influence of the selection of relevant text from the medical record on reliability, labeled as 'medical record extraction factor', and the quality of reporting by the elderly care physicians, a second reliability study on an independent sample (sample 2) was performed by three practicing elderly care physicians and a researcher. For this study a sample of 49 patient records from three DSCUs of two different care organizations that were not involved in the PROPER- study I was used.

Percentage of agreement was calculated and the Intraclass Correlation Coefficient for agreement (ICCagreement) was used for inter-rater reliability analysis [36] [41]. Considering that the magnitude of the ICCagreement is associated with prevalence [42], the proportion of positive agreement (both raters scored the item 'appropriate', both scored '0'), and the proportion of negative agreement (both raters scored the item 'inappropriate, both scored '1' or '2') per item were also calculated. The following interpretation of the ICCagreement was used: slight <0.20, fair 0.21-0.40, moderate 0.41-0.60, substantial 0.61-0.80, almost perfect 0.80-1.00 [43] [44].

Construction of a summated index score

To enhance the index' use in clinical research a sum score for the index, i.e. a summated index score was constructed. A summated index score creates a summary measure for appropriate PDU and improves its utility in clinical research [32], so that both individual PDs or multiple PDs used by a single

patient can be scored. For example, groups of PDs and patients can easily be compared on a particular moment or prospectively in time. The whole PROPER-study I sample, of 560 patients residing on DSCUs, was used for the construction of a summated index score (sample 3).

Expert panel 2 was asked to weigh the relative importance of each of the items, on a scale of 1 to 10, which we used to create the summated index score. This way, the relative contribution of the items to a summated index score could be calculated using mean item weights.
In applying a formative model inter-item correlations are not expected and internal consistency of the items is not implied [45][37]. However, excessive collinearity among items makes it difficult to separate the distinct influence of the items on the latent variable, the construct 'appropriateness'[35]. Considering that the summated index score is a measure for this construct, excessive collinearity among items could make an item redundant for the summated index score. In particular, if two items represent the same variance in the construct, one could be excluded from the index [35]. Thereto, the items were analysed for multicollinearity [35]. A common cut off threshold of 'below 10' of the Variation Inflation Factor (VIF) was used [46].
Reliability of the summated index score was estimated with ICCagreement, using the above-mentioned interpretation: slight <0.20, fair 0.21-0.40, moderate 0.41-0.60, substantial 0.61-0.80, almost perfect 0.80-1.00 [43] [44].

Construct validity
Sample 3 was also used for the study of construct validity. A gold standard for appropriateness of PDU for NPS is lacking, so that criterion validity could not be determined. Nevertheless, considering the above-mentioned multicollinearity analysis, each item's contribution to the summated index score, which is a measure of the construct, can also be interpreted as a validity indicator of the items' distinct influence on the construct [45]. In other words, high multicollinearity makes the individual contribution of an item to the construct's variance abundant.
        Although no structural validity can be explored in a formative model, the construct validity can be based on hypothesis testing [33]. Hence, the relative contribution of the items to the summated index score can be explored for consistency with hypothesized contributions to the mean summated index scores in a representative sample [33]. Assumed is that duration of therapy and indication will contribute the most to the mean summated index score, based on results found in previous studies which established that PDs are used persistently and indications are often missing [11][14].

Additionally, the assumed heterogeneity in the distribution of the summated index score was investigated. Similar to what was found in the summated score of the MAI [32] the summated index score is expected to be heterogeneous and positively skewed, in a representative sample. Skewness is assumed to be significant when the skewness divided by its standard deviation is above 1.96 (z-value). For this analysis the summated index score was divided into 7 categories, i.e. 0-10, 10-20, 20-30, 30-40, 40-50, 50-60 and 60-70.

RESULTS
Index development
Items for 'appropriateness of PDU for NPS in dementia'
Expert panel 1 excluded three of the ten MAI items, merged two into one and added one to develop the Appropriate Psychotropic drug use In Dementia (APID) index. Expert panel 1 made the following considerations:

The fourth item 'Are the directions correct?' was excluded, because correct directions, the route of administration and the relationship to food or liquids are relevant for many drugs, but was considered less relevant for PDs. The fifth item 'Are the directions practical?' was excluded based on the expert panel's opinion that the schedule and time of day of administration and its influence on the efficacy of the care are not regarded as a barrier in PD administration in nursing homes, since these are frequently discussed by physician and nurse, and hence adjusted. This makes the directions automatically practical. The item 'Is this drug the least expensive alternative compared to others of equal utility?' was judged irrelevant in (Dutch) nursing homes, since costs are a marginal factor in PD prescription. The panel used data of the costs derived from the 'Farmacotherapeutisch Kompas' [39].

The MAI items 'indication' and 'effectiveness' were merged in one item 'indication', given that the newly formed APID item 'indication' had guideline recommendations integrated. In other words, the item 'indication' scores appropriate when effective, i.e. according to the recommendations of drug utilization formularies.
Finally, a new item 'evaluation' was added, considering that evaluation of medication use is an important item for appropriate PDU [7].This resulted in a seven-item index, i.e. indication, evaluation, dosage, drug-drug interaction, drug-disease interaction, duplication and duration of therapy. Expert panel 2 deemed all seven items relevant for the construct.

CHAPTER 3

Scoring rules and instructions for medical record inspection
No structural changes in the initially formulated scoring rules were made
based on the results of the pilot tests. The response categories of the seven
items remained 0, 1 and 2. All items were scored based on the most recent
medical charts during data collection, except for the items 'indication' and
'evaluation'; for these items expert panel 1 formulated relevant periods of
medical record inspection. The periods were specified based on the
performed pilots.
Table 1 shows the general PD scoring rules and medical record inspection
periods for each of the items; see Appendix A for an example.

Table 1. General Psychotropic Drug scoring rules and medical record
inspection periods per item.

	Score 0	Score 1	Score 2
Indication	- Recommended by the VGPB and found in the medical record within 2 months after start of PD. - Recommended by the VGPB and found within 6 months after DSCU admission.	The typical PD not recommended by the VGPB, but another PD of similar ATC3 level.	Other or no indication found within the medical record inspection period.
Evaluation	- Within 2 weeks after starting medication? (for antidepressants within 8 weeks) - Within 6 months after DSCU admission	Within 6 months after start of PD	No evaluation found in the medical record inspection period.
Dosage	Recommend by VGPB or the SmPC.	Too low	Too high
Drug-drug interaction	No interaction indicated at the SmPC	Indicated as interaction at the SmPC. Although not recommended, when adequately monitored administration is possible.	Do not administrate, indicated at the SmPC.
Drug-disease interaction	No interaction indicated at the SmPC	Indicated as interaction at the SmPC. Although, not recommended, when adequately monitored administration is possible.	Do not administrate, indicated at the SmPC.

Duplication	No duplication in same grouped PD.	Duplication, without exceeding the total maximum combined dosage.*	Duplication, exceeding the total maximum combined dosage.*
Duration of therapy	- Recommended by the VGPB or SmPC. - Antipsychotics less than 3 months and 3 to 6 months, if a documented dosage reduction period is found.	Antipsychotics 3 to 6 months.	Exceeding recommendations

ATC3 level Anatomical Therapeutic Chemical classification 3 level / same grouped psychotropic drugs, DSCU Dementia Special Care Unit, PD Psychotropic Drug, SmPC Summary of Product Characteristic, VGPB Dutch association of ECP and community geriatricians (Verenso) guideline for problem behavior.

*The total maximum combined dosage was calculated based on each of the PDs percentage of their individual maximum dosage. The percentage was then summed up; if this exceeded a total of 100% a score 2 was given.

Item inter-rater reliability
The inter-rater reliability study (on sample 1), was conducted in September 2012 on 54 medical records from nursing home patients living on DSCUs, of which 18 males (33.3%) and 36 females (66.7%), with a mean age of 83 (62-96 years).

The inter-rater reliability of the seven individual items was moderate to almost perfect (ICCagreement 0.577-1), see Table 2.

Table 2. Inter-rater reliability study.

Item	Positive agreement	Dis-agreement	Negative agreement	Missing	Total Agreement	ICC agreement
Indication	.28	.23	.44	.05	.72	.775
Evaluation	.19	.30	.42	.09	.61	.577
Dosage	.86	.07	.07	0	.93	.698
Drug-drug interaction	.95	.05	0	0	.95	*
Drug-disease interaction	.84	.05	.07	.04	.91	.843
Duplication	.95	0	.05	0	1	1
Duration of therapy	.44	0	.53	.03	.98	.805

Positive agreement= proportion of positive agreement, both raters scored 0. Disagreement= proportion of disagreement, rater A and B disagreed, i.e. scored 0 and 1, 0 and 2 or 1 and 2. Negative agreement= proportion of negative agreement, both raters scored 1 or 2. Missing= proportion of missing data. Total agreement= proportion of total agreement, positive plus negative agreement. Interclass correlation coefficient for agreement (ICCagreement).
*No variance in ratings, so no ICCagreement can be estimated.

Data analysis was performed to identify the cause of disagreement between two raters. It was found that for the items 'indication' and 'evaluation', respectively 61,5% and 82.4% of the disagreement between raters was due to different information extraction from the medical records. For the items 'dosage', 'drug-drug interaction' and 'drug-disease interaction' all disagreements were due to medical record extraction factors. No disagreement was found for the items 'duplication' and 'duration of therapy', see Table 3.

Table 3. Cause of disagreement inter-rater reliability study.

Item	Indication	Evaluation	Dosage	Drug-drug interaction
Medical record extraction factor	61.5%	82.4%	100%	100 %
Application of scoring rules	38.5%	17.6%	0	0

Item	Drug-disease interaction	Duplication	Duration of therapy
Medical record extraction factor	100%	No disagreement	No disagreement
Application of scoring rules	0	No disagreement	No disagreement

An independent reliability study (using sample 2) was done to obtain insight into the medical record extraction factor, i.e. in differences between three practicing physicians and a researchers using the APID index. This study was conducted from September to November 2013. The average age of the subjects in sample 2 was 84 (20 males; 29 females), 64% used one or more PDs. It was found that there was one physician who scored the PDs significantly more appropriate than the researcher did on the item 'indication' (r =-0.13, p<0.1). No other significant differences were found. The specific physician had ready knowledge about the patient; both other physicians needed to use the medical record similar to the researcher to score the APID index and their indication score did not differ significantly.

Construction of a summated index score
Expert panel 2 weighted the items on a scale of 1 to 10. The items' mean weights are, in descending order; evaluation, indication, duplication, dosage, drug-disease interaction, duration of therapy and drug-drug interaction (see Table 4). Considering that the scores per item have a maximum of 2, the sum of the total weighted items, and thus the summated index score, had a range from 0 to 102.8, with higher scores indicating inappropriate use.

Table 4. Item weighting.

Items	Mean weights experts
Evaluation	9.6
Indication	9.4
Duplication	7.2
Dosage	6.7
Drug-disease interaction	6.6
Duration of therapy	6.1
Drug-drug interaction	5.8

For the multicollinearity analysis a sample of nursing home patients with dementia was used, the PROPER I sample 3. This study was conducted from January to June 2012. The sex distribution is 147 male (26.3%) and 413 female (73.8%), with a mean age of 85 (range 62-100 years). Three individual item scores were missing, therefore these PDs were excluded for the analysis of the summated index score.

All seven items were analysed for multicollinearity, the variance inflation factor (VIF) came to a maximum of 3.966, which is below the cut off threshold of 10. Hence, no multicollinearity issues were found and all seven items remained included in the index (see Table 5).

Table 5. Multicollinearity APID index.

VIF	Indication	Evaluation	Dosage	Drug-drug interaction	Drug-disease interaction	Duplication	Duration of therapy
Indication		1.993	3.966	3.966	3.966	3.966	2.985
Evaluation	1.499		2.983	2.984	2.983	2.983	2.984
Dosage	1.009	1.009		1.008	1.008	1.008	1.006
Drug-drug interaction	1.026	1.026	1.024		1.002	1.025	1.025
Drug-disease interaction	1.028	1.027	1.026	1.004		1.026	1.028
Duplication	1.004	1.004	1.003	1.004	1.003		1.004
Duration of therapy	1.504	1.998	1.991	1.998	1.998	1.998	

VIF = Variation Inflation factor

Using the newly formed summated index score, sample 1 (N=53) was used, as described above, to calculate the inter-rater reliability of the summated index score. It was found that this was substantial (ICCagreement 0.693). Absolute agreement was 37.2%.

Construct validity
As mentioned above**,** multicollinearity did not pose a problem for the construction of a summated index score based on the seven items, which also contributed to the importance of each of the seven items to the construct and thus the validity of the index.

For the items' contribution to the summated index score, as well as the distribution of the summated index score, sample 3 (N=560) was used, see description above.

As shown in Table 6 'indication', 'evaluation' and 'duration of therapy' contribute the most to the summated index score.

Table 6. Items mean weights, mean scores and mean weighted item scores.

Items	Mean weights experts	Mean score	Mean weighted item scores
Indication	9.4	1.07	10.06
Evaluation	9.6	0.89	8.54
Dosage	6.7	0.19	1.27
Drug-drug interaction	5.8	0.01	0.06
Drug-disease interaction	6.6	0.11	0.73
Duplication	7.2	0.09	0.65
Duration of therapy	6.1	0.83	5.06
Sum			26.4

The summated index score had a mean of 26.4 and a standard deviation of 15.7. Absolute scores range from 0 to 68.6, of which 10.4% of the PDs scored optimal, i.e. absolute zero. The summated index score was positively skewed (skewness= .280; standard deviation= .102; Z=2.75). The distribution of the single summated score was categorized in 7 ranges, see Table 7. Apparently, the summated index score shows a heterogeneous distribution; 18.2% had a score between 0-10, 20.5% between 10-20, 16.8% between 20-30, 24.8 % between 30-40 and 19.6% above 40.

Table 7. Distribution of summated index score.

Single summated score	Percentage	Cumulative percentage
0-10	18.2	18.2
10-20	20.5	38.7
20-30	16.8	55.6
30-40	24.8	80.4
40-50	9.5	89.9
50-60	8.9	98.8
60-70	1.2	100.0

DISCUSSION

Nursing home patients with dementia use PDs frequently and persistently, in particular for NPS. This study describes the development and validation of the first medication index specified to measure the appropriateness of this PDU. The MAI was adjusted for this purpose: relevant items of the MAI were selected based on the opinion of two independent expert panels. This study shows that all seven newly developed APID index items have good content validity and moderate to almost perfect inter-rater reliability.

The constructed summated index score is a summation of 7 weighted items that range from 0-102.8 per rated PD, from appropriate to inappropriate respectively. Furthermore, the summated index score is a good representation of the construct 'appropriateness of PDU for NPS in dementia', that shows promising construct validity.

Outcomes of the index development show that all seven items constructed by expert panel 1 were indicated as relevant for the construct 'appropriateness' by expert panel 2. Based on this result the APID index seems to be a valid measurement instrument for measuring appropriateness of PDU for NPS in dementia.

Results of the inter-rater reliability analyses show promising agreement on the individual items. The ICCagreement of the items are moderate to almost perfect. However, the proportion of positive and negative agreement should also be considered to make an informed assumption about the magnitude of the ICCagreement, given that it is related to the item's prevalence [42]. For example, although the item 'dosage' shows higher 'absolute' agreement than the item 'indication', the latter item has a higher ICCagreement. Hence, the items 'indication' and 'evaluation' have considerably lower 'absolute' agreement than the other items, but still have satisfactory ICCagreement, given that for these items the distribution of negative and positive agreement is balanced.

The results of the analysis of the cause of disagreement between two raters show that differences in information extraction are the major cause of disagreement. This implies that results of intra-rater reliability analysis are bound to be higher [36], considering that in repetitive measures by one rater the extraction of information is more consistent.

Hanlon et al. found a higher inter-rater reliability for the MAI [31]. However, this could be due to the fact that the MAI was administered using medical record abstracts in that study, provided by the same independent person. Other studies of the MAI's reliability found similar but also considerably lower reliability than what was found for the individual APID items [26]. Hence, the inter-rater reliability of the APID index items is promising, which could be

explained by the straightforwardness of its scoring rules; medical record content can be directly matched with formulary content and its corresponding scores.

Given that the APID index uses medical record reports for measuring appropriateness of PDU, this measure could also, next to a medical record extraction bias, be biased by the reporting quality. However, the independent reliability study found minimal differences between the researcher and the practising elderly care physician's administration of the APID index, which supports the concept of using medical records for an appropriate PDU for NPS index. Nevertheless, the results also show that the physician could have additional information about patients' PD indications that could influence the index' score.

The results of mean weights by expert panel 2 and the score range per individual item, i.e. 0-2, resulted in a summation of 7 weighted items that can range from 0-102.8 per rated PD, from appropriate to inappropriate, respectively. Additionally, it was found that all seven items contribute to the summated index score and that there were no multicollinearity issues. The reliability of the summated index score is substantial, however, it should be taken into account that this is not the same as the 'absolute' agreement between raters [41], which is important to consider if the index is to be used in clinical practise.

There is no gold standard to validate the index as a good measure for the construct 'appropriateness of PDU for NPS in dementia'. Nevertheless, the results of the expert panel 2 judgement and of the multicollinearity analyses show that all items contribute to the construct, indicating that the summated index score resembles the construct to be measured.

As predicted by the literature on appropriateness indicators [11][14][12], the results show that the items 'indication', 'duration of therapy' and 'evaluation' show a large contribution to the mean summated index score on a large group of patients, thus the overall inappropriateness of PDU. These results are in line with the mean weighting by expert panel 2 for items 'indication' and 'evaluation', combined with results of a multi-intervention study on all drugs used by elderly people that found that the items indication, duration and expense where most inappropriate using the MAI [47].

Furthermore, in the used data pool, the positive skewness found for the summated index score and its heterogeneous distribution makes the index applicable for the use in clinical research.

A limitation of this study involves the reliability of the 'clinical items' indication and evaluation, both have high disagreement between raters, largely due to

medical file extraction bias. Particularly, considering that these items have the highest weight in the summated index score. However, as mentioned before, a minimal difference between the researcher and the practising elderly care physician's administration of the APID index was found. This could imply that bad reporting results in inappropriate indications and evaluation scores. Nevertheless, without good reports about effectiveness (indications and evaluations) it is difficult for physicians to prescribe appropriately. Studies show that indications for antipsychotics are often unknown and can be used as a measure for its appropriate use [14][48]. Recently, indications are also added to the medication chart, what could improve reporting of indications.

Although the contextual domain of the construct, its hypothesised contributions to the average summated index score and the absence of multicollinearity are promising considering the validity of the index, further validity analysis should be explored in the future combining different types of validity and accumulating evidence when hypotheses are confirmed [33] [37]. Freeze describes two more steps, next to multicollinearity analysis, that can be taken in the study of nomological validity, i.e. the degree to which a construct should behave in relation to other constructs and the construct in isolation measured by reflective measures [37]. Additionally, in future research the MAI, which is not specified for PDU for NPS in dementia, could very well be used to investigate discriminant validity [37].
Furthermore, future research could study the APID index in relation to presence of NPS.
In addition, it should be taken into account that the APID index' content, i.e. the formularies for medication prescription and the SmPCs, are subject to revisions [26].In an ever-changing drug policy, nationally and internationally, formularies and the SmPCs are often revised, that is why the APID index should also be updated before every research trial. If items differ between nations, e.g. costs in the US, and are found relevant by local experts, these should also be added. Additionally, in the revisions mentioned above, validity should also be reconsidered.

Considering that the APID index is directly based on specific drug utilization formularies it could also be suited for clinical practise. However, that needs to be further explored.

CONCLUSION
The APID index and its individual items appear to be reliable and valid in clinical research. The summated index score and its item weights can be used in clinical research. Additionally, if one patient uses multiple PDs, individual PD scores can be added to create a patient's overall appropriateness of PDU

score. This also makes the APID index an applicable index to use in longitudinal research.

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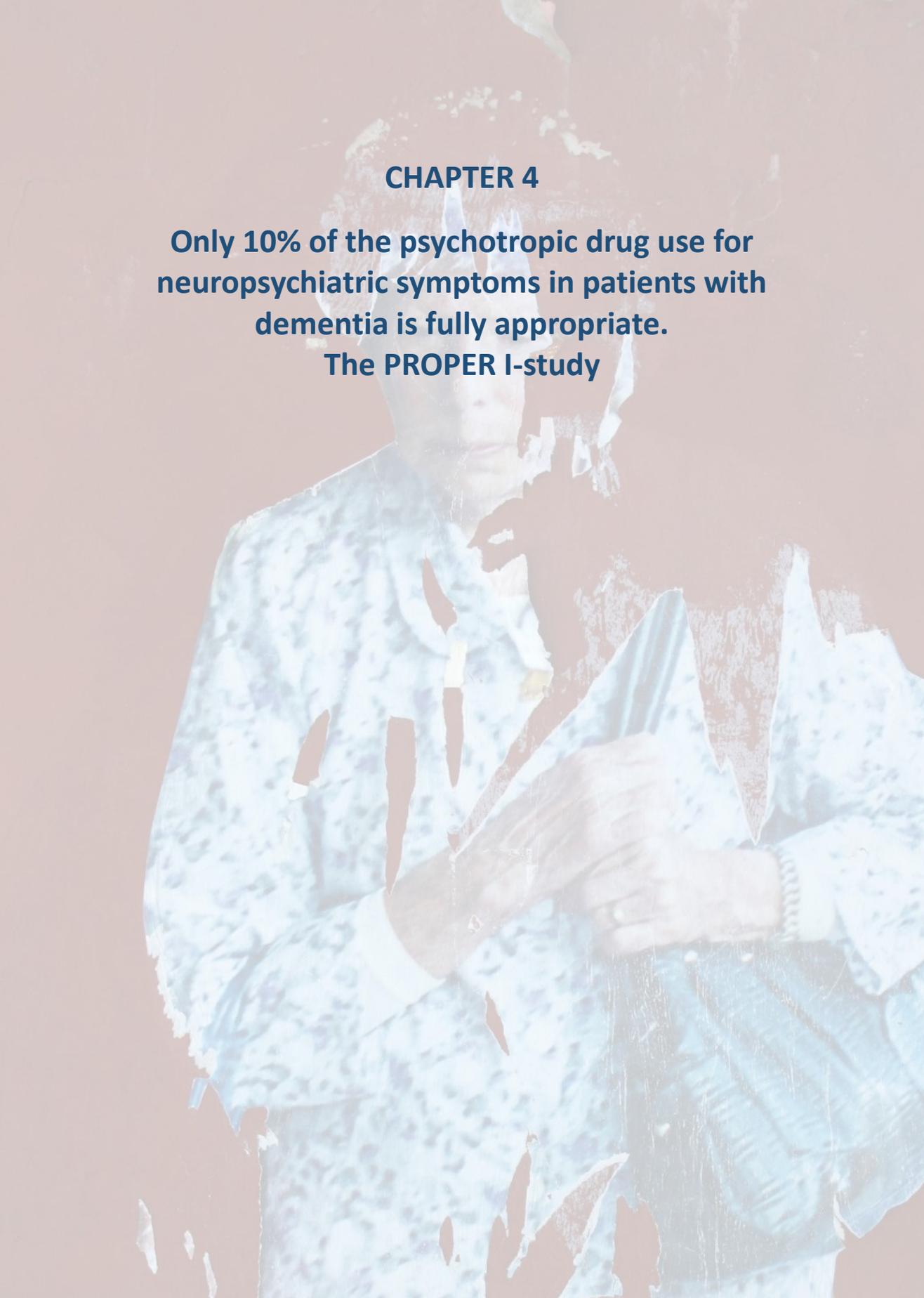
CHAPTER 4

Only 10% of the psychotropic drug use for neuropsychiatric symptoms in patients with dementia is fully appropriate.
The PROPER I-study

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ABSTRACT
Background
This study explores the appropriateness of psychotropic drug (PD) use for
neuropsychiatric symptoms (NPS) in nursing home patients with dementia.

Method
A cross-sectional study on 559 patients with dementia residing on dementia
special care units in Dutch nursing homes was conducted. Appropriateness of
PD use was assessed using the Appropriate Psychotropic drug use In Dementia
(APID) index. The APID index score is calculated using information about
individual PDs from patients' medical records. The index encompasses seven
(different) domains of appropriateness, i.e. indication, evaluation, dosage,
drug-drug interactions, drug-disease interactions, duplications and therapy
duration.

Results
A total of 578 PDs were used for NPS by 60% of the nursing home patients.
Indication, evaluation and therapy duration contributed the most to
inappropriate use. Ten per cent of the PDs scored fully appropriate according
to the APID index sum score, 36% scored fully appropriate for indication, 46%
scored fully appropriate for evaluation and 58% scored fully appropriate for
therapy duration. Antidepressants were used the most appropriately, and
antiepileptics the most inappropriately.

Conclusions
The minority of the PD use was fully appropriate. The results imply that PD use
for NPS in dementia can be improved; the appropriateness should be
optimised with a clinical focus on the appropriate indications, evaluations and
therapy duration.

Keywords
Behavioral and psychological symptoms of dementia (BPSD), dementia,
psychopharmacology.

INTRODUCTION

Psychotropic drugs (PDs) have limited evidence of efficacy for the treatment of neuropsychiatric symptoms (NPS) in dementia [1] [2] and there is substantial evidence on the risks, side effects and long-term inefficacy of PDs [3][4][5]. Antipsychotics, in particular, have been shown to cause adverse events, i.e. extrapyramidal symptoms, somnolence, increased risk of falls, stroke and mortality [3][6][7][8]. Anxiolytics and hypnotic drugs are associated with falls [9]. Therefore, the guidelines recommend psychosocial interventions as a first choice for treating NPS in dementia [10].

Despite this [10], psychotropic drugs (PDs) are frequently prescribed [11][12][1][13]. This concerns many different PDs, i.e. antipsychotics, anxiolytics, hypnotics, antidepressants, anti-dementia drugs and antiepileptics, the latter also being prescribed for NPS in dementia in the Netherlands [10].

The frequent use of PDs may raise questions about the appropriateness of prescription. There is some literature available supporting the hypothesis that PDs are used too long [14] [15][16], in duplicate prescription [1], and without proper indication [17][18]. Other aspects relating to a broader concept of appropriateness [19] are not available for PDs. This is important because appropriateness itself (and not frequency only) was found to be associated with a higher mortality [19].

Recently, we developed an instrument with seven domains of appropriateness [20] that gives us the opportunity to investigate the different domains of appropriateness simultaneously. Exploring appropriateness into more detail is imperative because a high frequency of psychotropic drug use (PDU) does not necessarily imply suboptimal drug therapy; to our knowledge, no studies relate the frequency and appropriateness of PDU.

The aim of this study is to assess the appropriateness of PDU for NPS in nursing home patients with dementia. More specifically, the research questions are: 1) How appropriate is the PDU for NPS in nursing home patients with dementia? 2) Which domains of appropriateness of PDU for NPS contribute the most to appropriate use? 3) Are there differences between PD types in the appropriateness of use? 4) Is there an association between the appropriateness of PDU and the number of PDs used per patient, dementia special care unit (DSCU), and elderly care physician?

METHODS

Study design

This study is part of the PROPER I study (PRescription Optimisation of Psychotropic drugs in Elderly nuRsing home patients with dementia); a cross-sectional study on the appropriateness of PDU for NPS in nursing home patients with dementia. The study was conducted from January to June 2012 and the data were collected from the medical records of Dutch nursing home patients with dementia residing in DSCUs. Data about PD prescriptions (dosage, drug-drug interactions, drug-disease interactions, duplications and therapy duration) was derived from the pharmacy part of the medical record; data about indications for the PD prescriptions and evaluation of effect/side effects of PD prescriptions was derived from the physician and nurse medical records in the time period PDs were started. The full study design is described elsewhere [21].

In this study, the unit of analysis is the prescribed PDs for NPS in a sample of nursing home patients. We did not include pro re nata use because the rationale for prescription may be different. Analyses were performed for the appropriateness (in general and per domain) of PDU in total, per PD group and per individual PD. Furthermore, the association of the appropriateness of PDU and the number of PDs used was analysed by investigating the association of appropriateness of PDU with the number of PDs used.

Assessment of appropriateness

The appropriateness of PDU was extracted from medical records and assessed using the Appropriate Psychotropic drug use In Dementia (APID) index [20]. The APID index is developed based on the items of the Medication Appropriateness Index [22] and is specifically suited for clinical studies evaluating the appropriateness of PDU for NPS in patients with dementia in nursing homes. Only medication administered for behaviour associated with dementia, sleep disturbance and delirium were scored with the APID index. Therefore, PDs that had a clear indication for psychiatric disorders other than dementia in the medical record, i.e. sleep disturbance and delirium, were excluded from scoring. If no clear indication was found in the medical record, it was assumed it was prescribed for NPS [20].

The APID index encompasses seven items corresponding with the seven different domains of appropriateness, i.e. indication, evaluation, dosage, drug-drug interactions, drug-disease interactions, duplications and therapy duration. Recommendations from national (Dutch) and international drug formularies are applied in order to score information about individual PDs; see the Appendix B for an example. The response categories of the seven domains are 0, 1 and 2 for fully appropriate, marginally appropriate and fully inappropriate prescribing. At the time of index development, an expert panel

weighted the relative importance of each of the domains on a scale from one to ten. This resulted in different theoretical ranges per domain as follows: indication (range 0-18.8), evaluation (range 0-19.2), dosage (range 0-13.4), drug-drug interactions (range 0-11.6), drug-disease interactions (range 0-13.2), duplication (range 0-14.4) and therapy duration (range 0-12.2). This way, the relative contribution of the domains could be incorporated into a sum score using mean weights. The APID sum score ranges from 0 (fully appropriate) to 102.8 (fully inappropriate) on individual PDs [20].

Psychotropic drugs were grouped using the Anatomical Therapeutic Chemical classification (ATC) [23]. Different PD groups had different theoretical sum score ranges, considering that antidepressants, as well as anti-dementia drugs, do not have a maximum therapy duration according to drug formularies. Therefore, these PDs cannot score as inappropriate for therapy duration. Moreover, other PD groups do not have a fully inappropriate drug-drug interactions score according to the APID index. This implies that there is a difference between the theoretical maximum sum score ranges of the different PD groups: antiepileptics (0-96.2), antipsychotics (0-102.8), anxiolytics (0-96.2), hypnotics (0-96.2), antidepressants (0-90.6) and anti-dementia drugs (0-84.8)[20].

Statistical analyses
First, the appropriateness of PDU in the total sample was determined by calculating the APID indexes mean sum scores (including range) and the percentage of PDs being prescribed fully appropriate (APID sum score = 0).

Second, the mean scores and their standard deviations per PD group and APID domain were calculated. The amount of use per PD group was also determined. The APID domains that contributed the most to the mean inappropriateness in the total sample, thus are the least appropriate, were analysed; the percentage of fully appropriate scores (score 0) was calculated for all APID domains taken together (APID sum score) and for each of these domains separately.

Third, the different outcomes were ranked using ranking (League) tables [24], i.e. outcomes are ranked according to the 95% CI of the mean APID sum score. Within the interval, the minimum ranking and maximum ranking were calculated for the different PD groups and ranked in ascending order. Additionally, per individual PD the amount of use in the total sample, the observed score ranges and mean APID sum scores were calculated. The percentages of fully appropriate scores were also calculated per individual PD for all domains taken together (APID sum score = 0), and for the least appropriate domains separately.
Fourth, to analyse the association between the appropriateness of PDU and the number of PDs used, the following calculations were performed: the

number of PDs used by individual patients, the average number of patients who receive one or more PDs per individual DSCU and the average number of patients who receive one or more PDs prescribed by individual elderly care physicians. When patients used more than one drug, the APID sum scores were averaged. The association was determined by calculating the 2-tailed Pearson correlation coefficient between the average number of use (percentage) and the mean APID sum score on patient, DSCU and elderly care physician level. A p-value <0.05 was considered statistically significant. Descriptive statistics and correlation calculations were performed by using IBM SPSS Statistics version 20.0. Ranking tables were created using Microsoft Excel, 2010 version (Microsoft Corporation, Redmond, WA, USA).

RESULTS

Participants' characteristics

The sample consisted of 559 patients living in 44 different DSCUs, cared for by 25 different elderly care physicians, of 12 Dutch nursing homes with 21 locations. There were 146 males (26.3%) and 413 females (73.8%) in the sample who had a mean age of 84 years (range 62-100). From the 559 patients, 338 used one or more PDs. These 338 patients used 578 PDs prescribed for NPS in total; three PDs were excluded from the analyses because of an incomplete APID-index score resulting in 575 PDs for the analyses**.**

1. *Appropriateness of total PDU*

The mean APID sum score for all 575 PDs was 26.6, ranging from 0 to 68.6; 9.6% of the PDs scored fully appropriate on the APID sum score.

2. *Appropriateness of PDU per domain and PD group*

The domains that contribute the most to the mean inappropriateness in the total sample are indication and evaluation for the PD groups antidepressant and anti-dementia drugs; indication, evaluation and therapy duration for anxiolytics, antipsychotics and hypnotics; and indication, evaluation and duplication for antiepileptics (Table 1). The domains indication, evaluation and therapy duration contributed to 89.5% of the mean inappropriateness, i.e. the APID sum score, in the total sample (not in Table). Therefore, these domains were further explored on their fully appropriate scores (score 0) per PD group and per individual PD.

Table 1. Appropriateness of use, defined by APID-scores, per domain and per psychotropic drug group, higher scores mean that they are less appropriate.

Psychotropic drug group	Indication Mean [SD]	Evaluation Mean [SD]	Dosage Mean [SD]	Drug-drug Interactions Mean [SD]	Drug- disease interaction Mean [SD]	Duplication Mean [SD]	Therapy duration Mean [SD]	Sum score Mean [SD]
Antidepressants N=167	10.9 [8.4]	9.2 [8.8]	0.4 [1.7]	0.1 [0.8]	1.3 [2.9]	0.4 [1.7]	0 [0]*	22.5 [14.5]
Anti-dementia drugs N=86	12.7 [8.9]	10.0 [9.2]	0.7 [2.9]	0 [0]	0.5 [1.7]	0.3 [2.2]	0 [0]*	24.7 [15.6]
Anxiolytics N=85	6.6 [9.0]	7.6 [8.4]	0.9 [3.5]	0 [0]	0 [0]	0.7 [2.4]	11.1 [3.6]	26.9 [14.6]
Antipsychotics N=147	9.0 [6.8]	7.7 [8.2]	1.7 [3.2]	0.2 [1.2]	1.0 [2.9]	0.7 [2.5]	8.8 [5.2]	29.1 [16.5]
Hypnotics N=76	10.3 [8.9]	7.6 [7.9]	3.5 [5.6]	0 [0]	0 [0]	1.0 [3.3]	8.3 [5.8]	30.8 [14.7]
Antiepileptics N=14	18.8 [0]	13.0 [8.1]	1.9 [3.1]	0.4 [1.6]	0.9 [2.4]	2.6 [3.6]	1.7 [4.4]	39.4 [10.1]
Total N=575	10.2 [8.4]	8.6 [8.6]	1.3 [3.4]	0.1 [0.8]	0.7[2.3]	0.7 [2.4]	5.0 [5.9]	26.6 [15.5]

SD= Standard Deviation.

* This psychotropic drug group could only score fully appropriate in this specific domain.

3. Appropriateness of PDU per PD group and per individual PD

Antidepressants are the most appropriately prescribed (95%CI, rank 1-3) and antiepileptics the most inappropriately (95%CI, rank 5-6) (Table 2). From all PDs, 36.1% had a fully appropriate score for indication, 45.6% a fully appropriate score for evaluation and 57.7% had a fully appropriate score for therapy duration. Further exploration of the scores showed that in 35.8% of the prescribed PDs no indication and in 52.7% no evaluation were found in the medical records (not in Table). Indications that were not registered accounted for 66.7% of the fully inappropriate indication scores, evaluations that were not registered accounted for 100% of the fully inappropriate evaluation scores (not in Table).

Table 2. Appropriateness of use, defined by APID-scores, per psychotropic drug group; higher scores mean that they are less appropriate.

Psychotropic drug group [theoretical range]	Sum score Mean [SD] [observed range]	N	Rank [95 % CI] Sum score	% sum score 0	% score 0 indication	% score 0 evaluation	% score 0 therapy duration
Antidepressants [0-90.6]	22.5 [14.5] [0- 51.2]	167	1 [1-3]	14.4%	31.1%	43.7%	100%*
Anti-dementia drugs [0-84.8]	24.7 [15.6] [0-52.4]	86	2 [1-5]	19.8%	27.9%	43.0%	100%*
Anxiolytics [0-96.2]	26.9 [14.6] [0-50.2]	85	3 [1-5]	4.7%	64.7%	50.6%	9.4%
Antipsychotics [0-102.8]	29.1 [16.5] [0-68.6]	147	4 [2-5]	5.4%	28.4%	48.3%	23.6%
Hypnotics [0-96.2]	30.8 [14.7] [0- 63.6]	76	5 [2-6]	2.6%	39.5%	46.1%	31.6%
Antiepileptics [0-96.2]	39.4 [10.1] [0-50.4]	14	6 [5-6]	0%	0%	21.4%	85.7%
Total [575], [0-102.8]	26.6 [15.5] [0-68.6]			9.6%	36.1%	45.6%	57.7%

*I= Confidence Interval, SD= Standard Deviation. * This psychotropic drug group could only score fully appropriate in this specific domain.*

The observed score range and the mean sum score per individual PD are shown in ascending order, only PDs that were used five times or more are shown (Table 3). The prescription of more than half of the shown individual

PDs scored not fully appropriate on all domains of appropriateness taken together, i.e. the APID sum score. Almost half of the shown individual PDs did not have a prescription that had a fully appropriate score on indication, i.e. score 0.

Table 3. Appropriateness of individual psychotropic drugs, defined by APID-scores, higher scores mean that they are less appropriate.

Individual psychotropic drugs, [observed range]		Sum score mean	N	% score 0 sum score	% score 0 indication	% score 0 evaluation	% score 0 therapy duration
Citalopram	[0-51.2]	19.1	83	28.9%	60.2%	45.8%	100%*
Zuclopentixol	[9.4-47.5]	20.5	6	0%	0%	66.7%	66.7%
Haloperidol	[0-50.2]	20.5	41	7.3%	42.9%	56.1%	40.5%
Memantine	[0-38.0]	21.7	32	28.1%	43.8%	40.6%	100%*
Escitalopram	[9.4-38.0]	21.9	7	0%	0%	42.9%	100%*
Trazodone	[0-38.0]	22.3	17	0%	0%	58.8%	100%*
Oxazepam	[0-50.2]	23.2	60	6.7%	78.3%	53.3%	8.3%
Rivastigmine	[0-44.6]	23.7	34	23.5%	29.4%	55.9%	100%*
Mirtazapine	[9.4-45.2]	25.4	26	0%	0%	38.5%	100%*
Risperidone	[0-64.6]	25.6	27	18.5%	70.4%	55.6%	22.2%
Venlafaxine	[9.4-38.0]	26.1	9	0%	0%	55.6%	100%*
Temazepam	[0-50.2]	27.9	37	2.7%	64.9%	45.9%	2.7%
Pipamperon	[9.4-57.4]	30.8	36	0%	0%	50.0%	8.3%
Paroxetine	[9.4-44.6]	31.0	14	0%	0%	21.4%	100%*
Galantamine	[9.4-52.4]	31.1	20	0%	0%	25.0%	20.0%
Melatonin	[0-51.4]	32.4	19	5.3%	21.1%	47.4%	100%*
Midazolam	[18.8-55.2]	35.5	6	0%	0%	33.3%	50.0%
Lorazepam	[12.2-50.2]	36.6	19	0%	42.1%	36.8%	5.3%
Olanzapine	[13.3-50.2]	36.8	5	0%	20.0%	40.0%	20.0%
Valproate	[18.8-45.2]	37.3	6	0%	0%	16.7%	100%*
Quetiapine	[16.3-68.6]	38.7	19	0%	10.5%	31.6%	10.5%
Clozapine	[15.5-63.4]	42.0	10	0%	10.0%	30.0%	20.0%
Total	[0-68.6]	26.6	575	9.6%	36.1%	45.6%	57.7%

This psychotropic drug could only score fully appropriate in this specific domain.

4. *Association of the number of PDs used with the appropriateness of PDU*

No significant association between the number of PDs used per patient and the mean APID sum score per patient was found (Pearson Correlation -0.016, Sig. (2-tailed) 0.769, N=338). Furthermore, no significant association was found between the average number of patients on a specific DSCU who received one or more PDs and the mean APID sum score on that DSCU (Pearson Correlation 0.030, Sig. (2-tailed) 0.582, N=44), nor between the average number of patients of the individual physician who receive one or more PDs and the mean APID sum score for that elderly care physician (Pearson Correlation 0.059, Sig. (2-tailed) 0.283, N=25).

DISCUSSION

To our knowledge, this is the first study to explore a broad range of relevant domains of appropriateness of PDU for NPS in nursing home patients with dementia.

We found that only ten per cent of the PDs scored as fully appropriate and that appropriateness was the least for the domains indication, evaluation and therapy duration. Dosage, drug-drug interactions, drug-disease interaction and duplications scored more appropriately. A potential explanation for this difference could be that, in Dutch nursing homes, domains such as drug-drug interactions are controlled by computerised processes and domains such as indication are dependent on the physicians' prescription policy. For instance, it appeared that in more than one-third of the psychotropic drugs no indication was found in the medical records. This confirms earlier findings that the majority of the patients in nursing homes have at least one drug prescribed of which the indication was unknown [17].

Antidepressants were prescribed the most appropriately, whereas antiepileptics were prescribed the most inappropriately. Another study [25] found that 18% of antipsychotics had appropriate indications and evaluations based on the prescription criteria. Our results showed low appropriateness rates regarding indications and evaluation not just for antipsychotics but also for all other PDs.

Furthermore, appropriateness was not associated with the number of PDs used per patient, the percentage of use on the separate units patients resided, nor the percentage of prescription of the individual physicians. Many studies describing the frequency of use [1][2] and prescription policies [14][26] focussed on reducing PDU [27]. However, our study suggests that the appropriateness and frequency of PDU may be unrelated; high rates of PDU do not necessarily reflect the inappropriate use of individual PDs. Therefore, it seems imperative not only to focus on absolute PDU, but also on its appropriateness. Nevertheless, both concepts are conjoined, two

inappropriate prescriptions still add up to less appropriate use than one inappropriate prescription. Implementation of tools that evaluate appropriateness in clinical practice may, therefore, lead to prescriptions that are more appropriate. The appropriateness of prescription might be improved by the implementation of tools such as the APID index in daily practice, which may, next to increased appropriateness, also reduce the frequency of use. Thereto, the APID index could be revised into a (self-) evaluation tool.

The absence of an association between frequency and appropriateness may also imply that the underlying factors of these constructs may differ. Factors related to frequency of use next to patient factors have been studied, e.g. bed capacity, under staffing, mindset and staff experience [28][29]. However, little is known about factors related to the appropriateness of PD prescription. This could be subject of further study.

A limitation of this study is that the results are based on medical record research, so that inappropriateness scores partly reflect a lack of reporting. However, as our former study shows, prescribers need good reporting to accurately review their own prescriptions [20], which implies that good reporting is a prerequisite for appropriateness and its measurement.

Another limitation of this study could be that the APID index does not detect under-prescription, thus this criterion was not included in our study results.

CONCLUSION
The appropriateness of the prescription of PDs for NPS in nursing home patients with dementia is rather poor; it should be optimised with a clinical focus on appropriate indications, evaluations and therapy duration.

CONFLICT OF INTEREST
None.

DESCRIPTIONS OF AUTHORS' ROLES
All authors declare that they have made a substantial contribution to: 1) conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) made the final approval of the version to be published.

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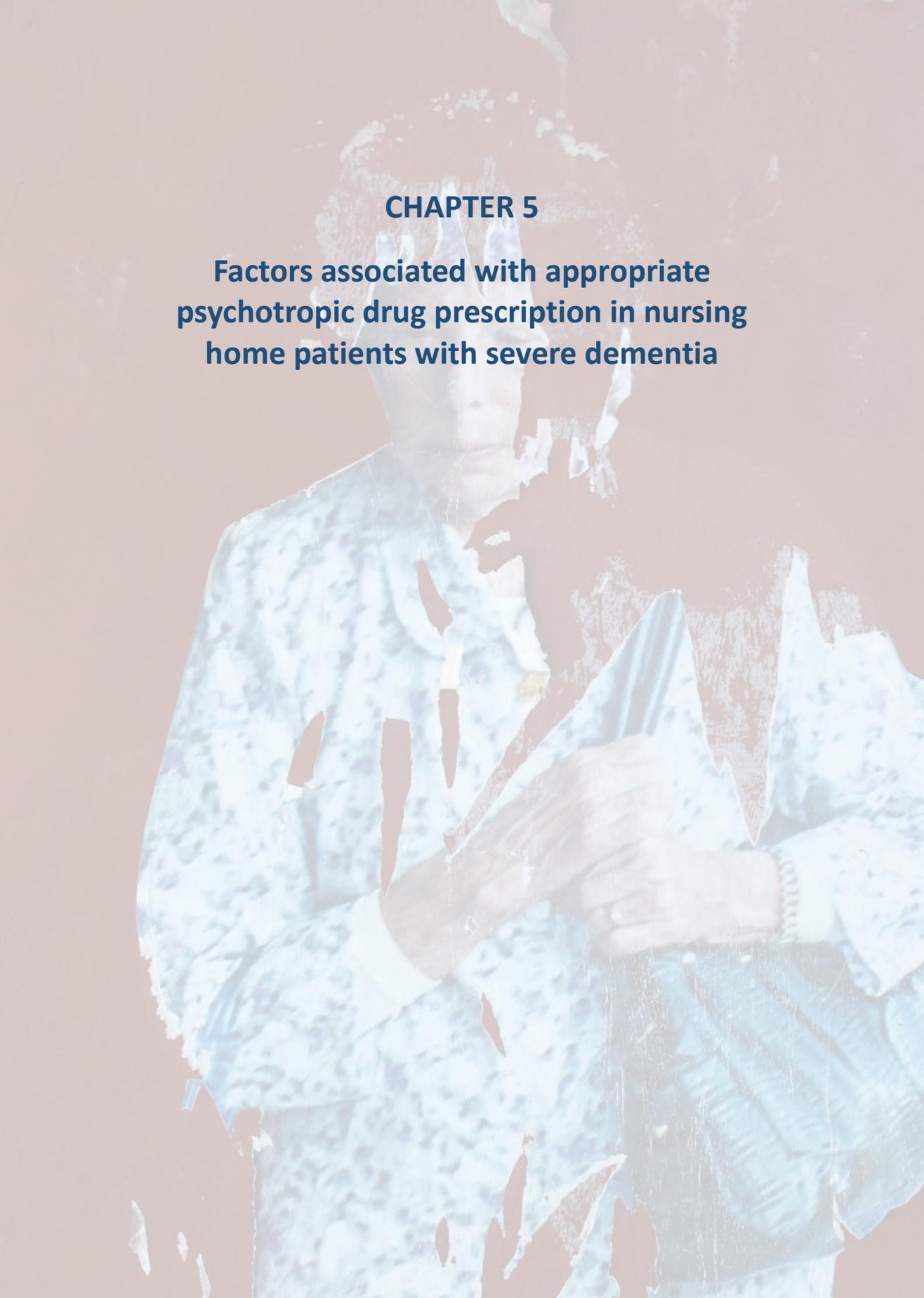
CHAPTER 5

Factors associated with appropriate psychotropic drug prescription in nursing home patients with severe dementia

CHAPTER 5

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ABSTRACT

Background

We studied the patient and non-patients factors of inappropriate psychotropic drug (PD) prescription for neuropsychiatric symptoms (NPS) in nursing home patients with severe dementia.

Methods

In a cross-sectional study, the appropriateness of prescriptions was explored using the Appropriate Psychotropic drug use In Dementia (APID) index sum score. This index assesses information from medical records on indication, evaluation, dosage, drug-drug interactions, drug-disease interactions, duplications, and therapy duration. Various measurements were carried out to identify the possible patient and non-patient factors. Linear multilevel regression analysis was used to identify factors that are associated with APID index sum scores. Analyses were performed for groups of PDs separately, i.e. antipsychotics, antidepressants, anxiolytics, and hypnotics.

Results

The sample consisted of 338 patients with a PD prescription that used 147 antipsychotics, 167 antidepressants, 85 anxiolytics, and 76 hypnotics. It was found that older patients and more severe aggression, agitation, apathy, and depression was associated with more appropriate prescriptions. Additionally, less appropriate prescriptions were found to be associated with more severe anxiety, dementia diagnoses other than Alzheimer dementia, more physician time available per patient, more patients per physician, more years of experience of the physician, and higher nurse's workload.

Conclusions

The association of more pronounced NPS with more appropriate PD prescriptions implies that physicians should pay more attention to the appropriateness of PD prescriptions when NPS are less manifest. Non-patient related factors are also associated with the appropriateness of PD prescriptions. However, especially considering that, some of these findings are counter-intuitive; more research on the topic is recommended.

Keywords

Dementia, psychopharmacology, neuropsychiatric symptoms.

INTRODUCTION

Psychotropic drugs (PDs) are prescribed for the treatment of neuropsychiatric symptoms (NPS) in dementia [1][2]. However, there is substantial evidence on the risks, side effects and long-term inefficacy of PDs [3][4]. That is why guidelines recommend a restricted, short-term use of PDs [5]. There is some literature available supporting the hypothesis that the duration of PD prescription is too long [6], with sometimes duplicate prescriptions [1][7], and without a proper indication [8]. Other aspects that relate to the broader concept of appropriateness have previously not been studied.

Different appropriateness measurement instruments that relate to the broader concept have been developed, e.g. STOPP/START criteria [9] and Medication Appropriateness Index (MAI) [10]. However, these are not specifically developed to measure the appropriateness of PD prescriptions for NPS in dementia.

      Recently, we developed the Appropriate Psychotropic drug use In Dementia (APID) index, which was derived from the MAI and was validated on a sample of (Dutch) nursing home patients with dementia [11]. The APID index measures the appropriateness of PD prescriptions for NPS in patients with dementia with a sum score that encompasses seven different domains of appropriateness: indication, evaluation, dosage, drug-drug interactions, drug-disease interactions, duplications and therapy duration. The APID index sum score showed to be reliable and valid for measuring appropriateness of PD prescriptions for NPS in dementia in nursing homes. Using the APID, we also found that the appropriateness of PD prescriptions and the frequency of PD use are unassociated, and thus independent concepts [12].

      Frequency of PD use varies considerably among nursing homes and units [13][14], which is only partly explained by the different prevalence rates of NPS among patients [15] [16]. The variation in PD use is also found to be related to differences in drug prescription policies [17], staff distress/workload [16], physical environmental factors, and the bed capacity [14].

Although several studies [16][18] investigated factors associated with PD use, we only found one study that reports about the factors associated with the appropriateness of PD prescriptions in dementia; it was found that the presence of behavioral symptoms and female gender were associated with more appropriate indications of benzodiazepines [19].

      Recently, we formulated a conceptual framework with four categories of factors with which the frequency and/or appropriateness of PD prescription were hypothesized to be associated, i.e. factors related to patient and non-patient factors (physician, nurse, and physical environment) [20].

Furthermore, in a previously conducted analysis about the appropriateness of PD prescriptions, the results indicated that the appropriateness of use differ per class of PD [12], and thus the factors related to appropriateness may also differ per class of PD, which compelled us to analyze antipsychotics (AP), antidepressants (AD), anxiolytics, and hypnotics separately. Some guidelines do not recommend benzodiazepine use (e.g. NICE guideline, 2016) and others do (e.g. BPSD guidance- NHS Cumbria; [21]). Benzodiazepines (oxazepam and lorazepam) are recommended for a maximum duration of four weeks in the Dutch guideline for NPS in patients with dementia, i.e. for agitation, anxiety and as adjuvant in case haloperidol has an insufficient effect on delirium. In addition, temazepam and zolpidem are recommended for sleep disorder for a maximum duration of two weeks [5]. The aim of the study was, therefore, to identify which patient and non-patient factors were associated with the appropriateness of prescriptions regarding four groups of psychotropic drugs.

METHODS
Design, setting, and sample
This study is part of the PROPER I study (Prescription Optimisation of Psychotropic drugs in Elderly nuRsing home patients with dementia) which is a cross-sectional mixed methods study that aims to identify the prevalence and appropriateness of PD prescriptions and its underlying factors. The study was conducted from January to June 2012. Thirty-six Dementia Special Care Units (DSCUs) divided over twelve nursing homes were needed based on our sample size calculations. The full study design is described elsewhere [20].

The local Medical Ethics Review Committee 'CMO Region Arnhem-Nijmegen' reviewed the study (number 2012/226) and pronounced that it was in accordance with the applicable rules in the Netherlands concerning the review of research ethics committees and informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Measurements
Appropriateness of psychotropic drug prescriptions
Appropriateness was explored using the APID index. This index sum score ranges from 0-102.8 where a lower score indicates a more appropriate PD prescription. The APID index sum score is based on seven domains, i.e. indication, evaluation, dosage, drug-drug interactions, drug-disease interactions, duplications and therapy duration, which are weighted for their contribution to the construct [11].

PD prescription was grouped according to the Anatomical Therapeutic Chemical (ATC) classification into: antipsychotics (APs) (N05A), antidepressants (ADs) (N06A), anxiolytics (N05B), and hypnotics (N05C)(Nordic Council on Medicines, 1990).

Factors associated with appropriate psychotropic drug use

The PROPER-I dataset contained 115 possible variables (including subscores) associated with frequency and/or appropriateness. Because it was estimated that a maximum of 28 factors could be included in the analyses, 28 variables were selected as guided by our framework [20]. Based on the existing evidence for the factors being associated with the appropriateness of PD prescriptions and on their clinical expertise, the authors rated the relevance of the factors and reached consensus on what would be the 28 most relevant factors. It appeared that factors were selected from three of the four categories of the framework, i.e. patient-related factors, physician-related and nurse-related factors. There were no physical environment-related factors selected as these factors showed lack of variation in the participating nursing homes.

The following instruments were used to assess information about these factors clustered within three categories:

1) Patient-related factors

Twelve patient-related factors were selected. We collected data about age, sex, length of stay at DSCU and dementia type (i.e. Alzheimer's dementia (AD), Vascular Dementia (VaD), mixed AD/VaD, and other dementia (including 'not otherwise specified').

The severity of NPS was assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q)[23]. The 12-item NPI-Q evaluates the severity of 12 NPS in the previous month on a 4-point scale ranging from 0 (absent) to 3 (severe). Symptoms were grouped into five clinically meaningful categories similar to what was done for this instrument's nursing home version [24], i.e. psychosis (hallucinations and/or delusions), agitation (agitation, disinhibition, and/or irritability), depression, anxiety and apathy.

Agitation/aggression was further assessed with the Cohen-Mansfield Agitation Inventory (CMAI)[25][24]. The CMAI consists of 29 agitated behaviors to be scored for the frequency of occurrence in the previous 2 weeks on a 7-item scale ranging from 1 (never) to 7 (several times per hour). We grouped the symptoms into 3 categories: physical aggression (range 8 to 56), physically nonaggressive behavior (range 7 to 49), and verbally agitated behavior (range 4 to 28)[25].

2) Physician-related factors

Five physician-related factors were selected. The attitude of physicians toward caring for people with dementia was measured with the Approaches to Dementia Questionnaire (ADQ)[26]. The ADQ contains 19 statements to be scored on a 1 to 5 Likert scale, resulting in a total score ranging from 19 (negative attitude) to 95 (positive attitude). Additionally, we registered the

number of years working as a physician. The physician's availability in minutes per patient per week, the number of patients per physician and the physician's reported time spent weekly on patient care.

3) Nurse-related factors

Eleven nurse-related factors were selected. The experienced nurse distress was assessed with the 12-item NPI-Q, which measures distress and NPS simultaneously, in the previous month on a 4-point scale ranging from 0 (absent) to 3 (severe). The symptoms were, again, grouped into the above-mentioned five clinically meaningful categories. The staff strain with regard to caring for patients with dementia was measured with the Strain in Dementia Care Scale (SDCS) [27]. The SDCS consists of 27 items on personal situations, thoughts or feelings. Items are weighted in terms of frequency (on a 4-point scale), multiplied by the amount of stress (on a 4-point scale); the total score, which was used for this study, is calculated by dividing the total summarized score with the amount of items included (possible range: 1–16). In addition, the Satisfaction with Patient Contact subscale from the Maastricht Work Satisfaction Scale for Healthcare (MAS-GZ) was assessed [28], which consists of 3 items on mutual liking between patients and nurse, each ranging from 1 (very unsatisfied) to 5 (very satisfied) and a mean subscore (range 1 to 5). To measure the attitude of nurses toward caring for people with dementia, the above-mentioned ADQ was used. The nurses' workload was assessed with a Dutch scale on job strain (Werkdruk de Jong) [29]. This instrument consists of 8 statements regarding the presence of demanding aspects of the job with a 5-point response scale resulting in a total score ranging from 1 (never) to 5 (always).

Furthermore, we obtained the nurse/patient ratio during the day (morning, afternoon, and evening) and the total number of different caregivers (e.g. nurses, supporting personnel) at the DSCU for assessing continuity in care.

Procedures

Variables were either collected per individual patient (PD prescriptions, patient characteristics, NPI-Q and CMAI) or per DSCU (all other variables). PD prescriptions were retrieved from the actual medication list, patient characteristics from the patient's charts, and nursing home characteristics (nurse/patient ratio, number of patients per DSCU, and number of different caregivers) were retrieved from the DSCU's team manager. All other data were collected web-based and completed by physicians or nurses. The maximum time window between the appropriateness measurement of PDs and the measurement of possibly related factors was 6 weeks.

Statistical analyses

Sample characteristics were calculated, i.e. age, sex, number of patients that had a PD prescription, DSCUs, nursing homes and physicians, dementia diagnosis, number of PDs used in total and range of APID index sum score.

Both unilevel and multilevel multivariate linear regression analyses were performed with the APID sum score as a dependent variable. Prior to analyses, to control for (problems of) multicollinearity (in analysis and interpretation), factors were analyzed for multicollinearity and if so, factor analysis was applied to find underlying latent variables.

The APID sum score was calculated separately for the four different PD groups. If patients used more than one prescription in one of the four PD groups, the APID index sum score was averaged.

Using all 28 preselected variables in a multivariate multilevel modeling would result in overfitting for each of the PD groups (i.e. results would likely be too specific for this dataset and hence not generalizable). To avoid overfitting, we used the 10-patients-per-predictor (N=10) rule of thumb [30] to determine, for each type of PD, the maximum number of predictors to be used.

To reduce the 28 preselected variables to this maximum number of variables, the following pragmatic approach was taken, for all four types of PD separately, with multivariate unilevel preselection:

Step 0) We fitted a model with all 28 predictors ('the benchmark model'), acknowledging that this would result in an overfitted model (and should therefore not be interpreted), but would at least give the maximum amount of variance ('the benchmark') that could be explained for the type of PD considered. In subsequent steps we tried to come as close as possible to this benchmark, while keeping the number of predictors below the maximum allowed by the N=10 rule of thumb.

Step 1a) We preselected independent variables with the most influence in a unilevel (i.e. on patient-level) linear regression model via stepwise backward likelihood ratio selection with entry p<0.05, removal p<0.10. If step 1a resulted in a model with too many variables according to the N=10 rule of thumb or if step 1a resulted in a model with a significantly worse fit compared to the 'benchmark model' we then applied step 1b). The occurrence of a worse fit was guided by a more than 10% lower R^2 (explained variance) compared to the benchmark (model) and/or statistical significant worse fit by using the 2-loglikelihood ratio test.

Step 1b) Best subset unilevel linear regression was used to choose a selected number of variables not based on the p-value of individual variables but by comparing the fit of subsets (combinations of the 28 variables). For each amount of variables (1, 2, ..., 28 variables), the combination (subset) with that number of variables that has the highest R^2 was identified ('best subset' with that amount of variables). Out of the best subsets with 1, 2, .., 28

variables, the smallest subset of variables explaining 90% or more of the R^2 from the benchmark model (see step 0) was considered as a model having good fit and no overfitting.

        Step 2) The preselected variables were put together in the final *multilevel* linear regression model.

        For all analyses, we used IBM SPSS Statistics, Version 22.0 and SAS 9.2 (SAS Institute, Inc., Cary, NC). Variables that had 10% or more missing cases were excluded from the analyses.

RESULTS

Table 1. Sample characteristics.

Characteristics of nursing home patients	
Mean age in years (range)	84 years (range 62-100)
Sex, female in percentage	73.8%
Number of patients that had a psychotropic drug prescription	338
Number of DSCUs	44
Number of nursing homes	12 organizations with 21 locations
Number of physicians	25
Diagnosis of dementia (percentage)	
Alzheimer's dementia	186 (33.3%)
Vascular dementia	92 (16.5%)
Mixed Alzheimer's/vascular dementia	62 (11.1%)
Other dementia	219 (39.2%)

Number of psychotropic drug prescriptions	
Antipsychotics	147
Antidepressants	167
Anxiolytics	85
Hypnotics	76

PDs were prescribed to 338 patients (see Table 1 for sample characteristics) in duplicate prescriptions: 147 APs, 167 ADs, 85 anxiolytics, and 76 hypnotics were used [12]. When applying the N=10 rule of thumb (1 factor/determinant per 10 incident cases) on the prescriptions per patient [31], 14, 16, 8, and 7 variables could be used in the final models, respectively. In table 2, the abovementioned multivariate unilevel preselection method of variable

reduction was described, the final models are shown in bold. The APID index sum score ranged from 0 to 68.6.

Table 2. Unilevel preselection method of variable reduction in a multivariate regression model.
Based on unilevel linear regression modelling via stepwise backward selection (step 1a) and best subset regression (step 1b) a selection of variables for multilevel analyses were made for four psychotropic drug group models (final models are shown in bold with asterisk). [1]

Model	All the 28 variables 2-loglikelihood/ R^2	Step 1a: Backward selection No. variables/ 2-loglikelihood/ R^2	Significant difference backward selection with all 28 variables model	Step 1b: Best subset regression No. variables/ 2-loglikelihood/ R^2	Significant difference best subset with all 28 variables model
Antipsychotics	1084.62 $R^2= 0.29$	5/ 1128.06/ $R^2= 0.18$	Difference = 43.44 S (df 23, X^2 = p<0.01)	**13/ 1092.28/ $R^2= 0.27$ ***	Difference = 7.66 NS (df 15, X^2 = p>0.25)
Antidepressants	1259.10 $R^2= 0.24$	**3/ 1283.54/ $R^2= 0.15$ ***	Difference = 24.44 NS (df 25, X^2 = p>0.25)	-	-
Anxiolytics	638.15 $R^2= 0.36$	**5/ 658.06/ $R^2= 0.25$ ***	Difference = 19.91 NS (df 23, X^2 = p>0.25)	-	-
Hypnotics	535.27 $R^2= 0.49$	A model with 9 variables was found; this is too many according to the rule of thumb (N=10). The best subset of 7 was used.		**7/ 567.96/ $R^2= 0.35$ ***	Difference = 32.69 S (df 21, X^2 = p<0.05)

***Final model**, R^2= explained variance, S= significant, NS= not significant, no. =number.
[1] *For the four different models R^2 and 2-loglikelihoods were calculated and analyzed for significant difference with the hypothetical full models with all 28 variables:*
- For antipsychotics, stepwise backward selection resulted in a model that was significantly different from the hypothetical full model and, therefore, best subset regression was performed; that resulted in a model with 13 variables and was found not significantly different from hypothetical full model.
- For antidepressants, stepwise backward selection resulted in a model with 3 variables, which was found to be not significantly different from the hypothetical full model.

- For anxiolytics, stepwise backward selection resulted in a model with 5 variables, which was found to be not significantly different from the hypothetical full model.
- For hypnotics, a model with 7 variables was chosen considering the 10-patients-per-predictor rule of thumb, but this model was significantly different from the hypothetical full model.

Multilevel analyses

No multicollinearity was found between variables. Multilevel analyses with levels DSCU and location (step 2) were performed for antipsychotics, antidepressants, anxiolytics, and hypnotics.

In the antipsychotics group, the following statistically significant associations were found: High CMAI physical aggression and older patient age were associated with low APID index sum scores; high NPI anxiety severity and physician patient care in minutes per week with high APID index sum scores. For the antidepressants group: High NPI apathy severity and high NPI depression severity were associated with low APID index sum scores. For the anxiolytics group: High CMAI physical aggression was associated with low APID index sum score; type of dementia other than Alzheimer's dementia and high job strain of nurses were associated with high APID index sum scores. Finally, for the hypnotics group: High NPI agitation severity was associated with low APID index sum score; high number of patients per physician and more years of experience for physicians were associated with high APID index sum scores (Table 3).

Table 3. Multilevel models on the factors of the appropriateness of psychotropic drug use for antipsychotics, antidepressants, anxiolytics, and hypnotics. Variables are presented by patient-related, physician-related and nurse-related from top to bottom. More indicates a lower APID index sum score, thus a factor associated with more appropriateness. Less indicates a higher APID index sum score, thus a factor associated with less appropriateness.

	Antipsychotics	p-value	Antidepressants	p-value	Anxiolytics	p-value	Hypnotics	p-value
1	**Patients' age**	**More p 0.02***	**NPI category apathy severity**	**More p 0.00***	**Type of dementia Mixed AD/VaD in comparison to AD**	**Less p 0.04***	Time (months) on this DSCU	Less p 0.16
2	Patients' sex	More p 0.26	**NPI category depression severity**	**More p 0.01***	**CMAI (physical) aggression**	**More p 0.03***	**NPI category agitation severity**	**More p 0.01***
3	Time (months) on this DSCU	Less p 0.26	Nurse ADQ Total score	Less p 0.08	Number of patients per physician	Less p 0.37	NPI category apathy severity	More p 0.07
4	**NPI category anxiety severity**	**Less p 0.01***			Nurse SDC Total score	More p 0.10	CMAI Verbal agitation	Less p 0.09
5	NPI category depression severity	More p 0.14			**Nurse job strain**	**Less p 0.04***	**Number of patients per physician**	**Less p 0.03***
6	**CMAI (physical) aggression**	**More p 0.00***					**Physicians experience (years)**	**Less p 0.01***
7	CMAI motor agitation subscale	More p 0.17					Nurse_patient_ratio_ daytime	More p 0.13
8	Physician ADQ Total score	More p 0.20						
9	**Physician pt. care in minutes per week**	**Less p 0.03***						
10	Number of patients per physician	Less p 0.09						

		Antipsychotics	p-value	Antidepressants	p-value	Anxiolytics	p-value	Hypnotics	p-value
11	Nurse ADQ Total score	Less p 0.30							
12	Nurse WDJ Total score	More p 0.24							
13	Nurse_patient_ratio_daytime	Less p 0.42							

In bold with asterisk = a significant effect was found, Neuropsychiatric Inventory- Questionnaire (NPI-Q), Cohen-Mansfield Aggression Inventory (CMAI), Approaches to Dementia Questionnaire (ADQ), Strain in dementia Care (SDC), the Maastricht Work Satisfaction Scale for Healthcare 'Maastrichtse Arbeidssatisfactie Schaal voor de Gezondheidszorg' (MAS-GZ), AD= Alzheimer disease, VaD= Vascular Dementia, DSCU=Dementia Special Care Unit.

DISCUSSION
Main findings
To our knowledge, this study is the first that investigates the factors associated with the appropriateness of PD prescriptions for NPS in nursing home patients with severe dementia on a broad range of appropriateness indicators summarized in one index score. We found that patient factors particularly influence appropriateness. Psychotropic drugs were more appropriately prescribed in patients with higher levels of NPS, older age, and other types of dementia than Alzheimer's dementia. Patient factors accounted for eight out of twelve of the found associations in the four different PD groups.

Regarding antipsychotics, the severity of aggression was associated with appropriate prescriptions, in antidepressants this was the severity of apathy and depression, in anxiolytics it was the severity of aggression, and in hypnotics it was the severity of agitation. Since the inappropriateness of a prescription is mainly based on poor indications, evaluations, and therapy durations [12], these findings signify that when NPS were less pronounced, appropriate indications for these symptoms were missing, while evaluations of these prescriptions are lacking and the therapy continues.

Next to patient factors, of the several non-patient factors, one physician- and one nurse-related factor appeared to be associated with the appropriateness of PD prescriptions.

In the hypnotic group, prescriptions were less appropriate when the prescribing physician had a higher caseload. In the anxiolytic group, we found that prescriptions were less appropriate when nurses experienced more workload. This latter finding is in line with previous studies indicating that physicians feel more pressure to prescribe when the burden of nurses is high [14][15], which may result in less appropriate prescriptions. Additionally, when the workload is high, the pharmacological treatment of NPS compared to psychosocial treatment, which is the recommended intervention [5][32], could be considered as less time consuming. Therefore, pharmacological treatment is often preferred, while there is less time to appropriately evaluate and stop these prescriptions.

Nevertheless, other factors associated with the appropriateness of PD prescription were counter-intuitive, and possibly a result of multiple testing: In the antipsychotics group, severe anxiety and physicians' time available per patient were associated with less appropriate prescriptions. Moreover, it was found that the more experience a physician had the less appropriate the hypnotics were prescribed.

As mentioned before, little was known on this topic. Recently more relevant research has been published and it was found that large numbers of physicians working in one organization could result in an inappropriate prescription of antipsychotics [33]. Another study found that after long-term care admission, new antipsychotic use was just as strongly associated with social factors as clinical factors [34]. However, these studies did not address a large variety of potential patient and non-patient factors associated with the broader concept of appropriateness, i.e. on multiple items of appropriateness and in different PD groups.

Methodological considerations

A limitation of this study was that including all the possibly relevant factors, as collected for the PROPER-I study [20], led to a large number of factors compared to the number of patients, which could lead to an overfit of the statistical models. In order to control for this, we had to make a selection. Due to this selection, 28 of the in total 115 collected factors were used for analyses. Many of the for PROPER I collected factors were not included, considering that these were less relevant or were covered by other measures based on a conceptual framework. In this process relevant factors might have been lost, e.g. physical environment-related factors. Additionally, this selection was performed by a sample of clinical experts from one single country, which can also be concerned as a limitation.

Furthermore, as mentioned before, we used multiple tests on the selected variables, which could have resulted in factors found coincidentally. Therefore, these associations might be clinically irrelevant and should be interpreted with caution.

This Dutch study was performed on so called DSCUs with trained elderly care physicians as the responsible physician, therefore the results should be generalized to other health care systems with carefulness. In addition, the dependent variable was the APID index sum score. Prior to this study, the same patients' records were used, by the same research team, in the development and validity study of the APID index. Therefore, uncertainty exists about the generalizability of the results to other samples, which could be considered as a limitation of the study; the APID index should be used in other samples to test the external validity of the results.

Furthermore, DSCUs are specialized in treating patients in advanced stages (Global Deterioration Stages 4 - 7, primarily 6 - 7) of dementia. In this study only patients residing on these units were included, therefore, patients included in this study all had severe levels of cognitive impairment. Although inappropriate prescriptions are likely to affect cognition [35]. Due to the assumed floor effect (insufficient variance) we did not include an instrument

to detect cognitive impairment and therefore did not obtain information about the association between cognitive impairment and the appropriateness of PD prescriptions. Moreover, the stage of dementia and thus the level of cognitive impairment is unlikely to predict the appropriateness of PD prescriptions independent of behavior, which compelled us to obtain information about the extent of NPS.

This study was conducted in single country and 12 nursing homes, that only involved people with severe dementia, which is typical for Dutch nursing homes. However, the appropriateness of PD prescriptions is a worldwide challenge [36][37], potentially, these results may be generalizable to other countries with similar health care systems.

CONCLUSIONS AND CLINICAL IMPLICATIONS

We found that there is an association between more pronounced NPS and more appropriate PD prescriptions in patients with severe dementia, which implies that physicians should be especially aware of the appropriateness of prescription when NPS are less manifest. Carefully recording and regularly evaluating these prescriptions could prevent inappropriateness. Obviously, patient factors influence PD prescription. Physician and nurse factors seem to also influence the appropriateness of PD prescriptions, and thus guideline adherence regarding appropriate indications, evaluations, and therapy durations. However, some of these findings are counter-intuitive and thus unclear; more research on the topic is recommended.

To minimize these influences, standardization and thus guideline adherence is advised.

CONFLICT OF INTEREST

None.

DESCRIPTION OF AUTHORS' ROLES

All authors declare that they have made a substantial contribution to: 1) conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) made the final approval of the version to be published.

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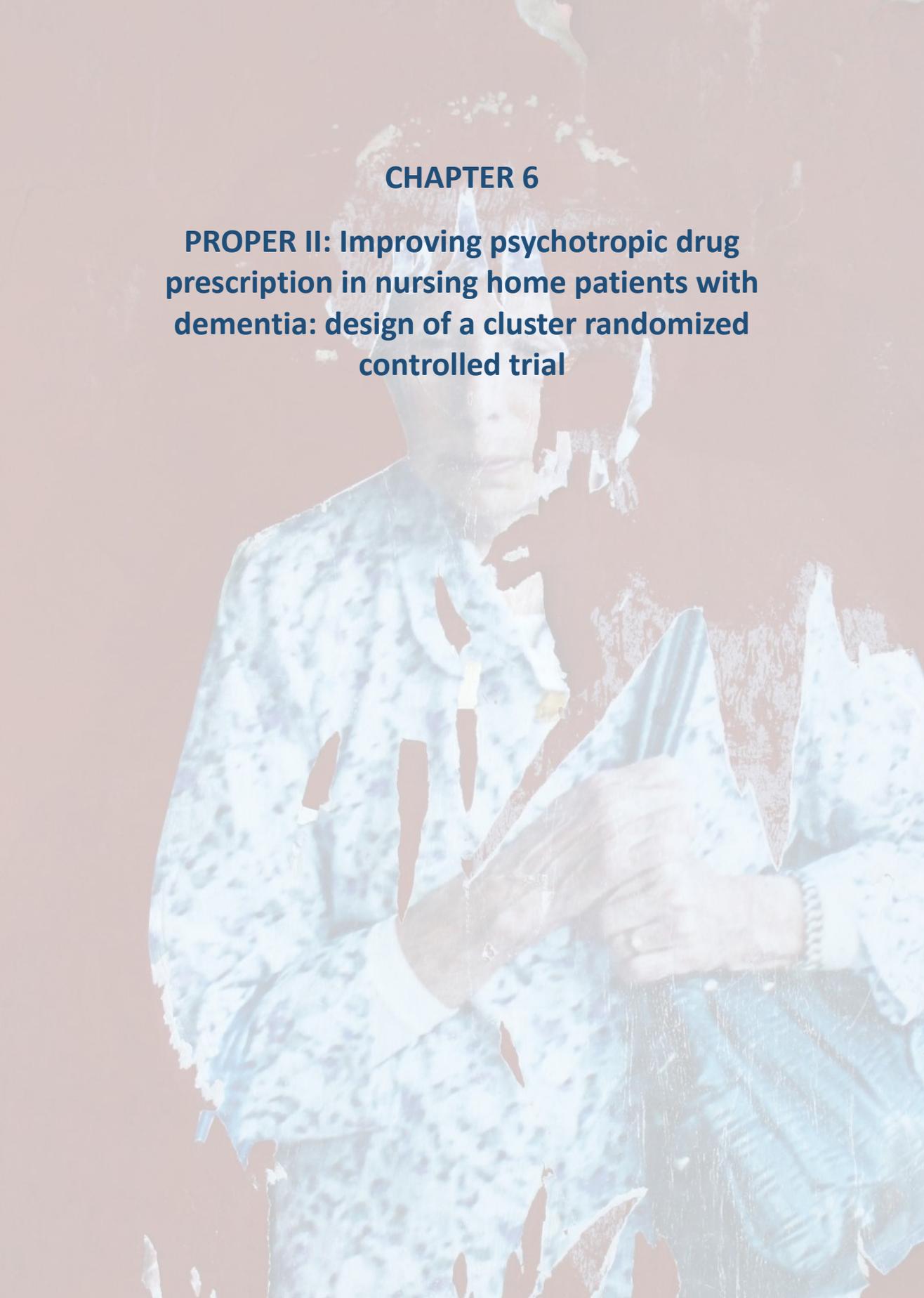
CHAPTER 6

PROPER II: Improving psychotropic drug prescription in nursing home patients with dementia: design of a cluster randomized controlled trial

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ABSTRACT
Background
Neuropsychiatric symptoms are highly prevalent in nursing home patients with dementia. Despite modest effectiveness and considerable side effects, psychotropic drugs are frequently prescribed for these neuropsychiatric symptoms. This raises questions whether psychotropic drugs are appropriately prescribed. The aim of the PROPER (PRescription Optimization of Psychotropic drugs in Elderly nuRsing home patients with dementia) II study is to investigate the efficacy of an intervention for improving the appropriateness of psychotropic drug prescription in nursing home patients with dementia.

Methods/Design
The PROPER II study is a multi-center cluster randomized controlled, pragmatic trial using parallel groups. It has a duration of eighteen months and four six-monthly assessments. Six nursing homes will participate in the intervention and six will continue care as usual. The nursing homes will be located throughout the Netherlands, each participating with two dementia special care units with an average of fifteen patients per unit, resulting in 360 patients. The intervention consists of a structured and repeated multidisciplinary medication review supported by education and continuous evaluation. It is conducted by pharmacists, physicians, and nurses and consists of three components: 1) preparation and education, 2) conduct, and 3) evaluation/guidance. The primary outcome is the proportion of patients with appropriate psychotropic drug use. Secondary outcomes are the overall frequency of psychotropic drug use, neuropsychiatric symptoms, quality of life, activities of daily living, psychotropic drug side effects and adverse events (including cognition, comorbidity, and mortality). Besides, a process analysis on the intervention will be carried out.

Discussion
This study is expected to improve the appropriateness of psychotropic drug prescription for neuropsychiatric symptoms in nursing home patients with dementia by introducing a structured and repeated multidisciplinary medication review supported by education and continuous evaluation.

Trial registration
Netherlands Trial Registry (NTR): NTR3569.

BACKGROUND
Neuropsychiatric symptoms (NPS) are highly prevalent in and burdensome for nursing home patients with dementia. Studies show prevalence rates of clinically relevant NPS of over 70% [1][2], and a cumulative two-year prevalence of even 97% [3]. NPS comprise a wide range of heterogeneous symptoms including delusions, hallucinations, agitation/aggression, depression, apathy, euphoria, anxiety, disinhibition, irritability, and aberrant motor behavior, which are frequently treated with psychotropic drugs. It is known that the efficacy of psychotropic drugs is limited and that their use is associated with considerable side effects such as extrapyramidal symptoms, somnolence, and increased risk for stroke, pneumonia, and mortality [4-7].

Nevertheless, the prevalence of psychotropic drug use (PDU) among nursing home patients with dementia is high with rates ranging from 48 to 66% [8-10]. Moreover, there is a risk for long-term use of psychotropic drugs whereas prescription for only a short period of time is recommended [4][11]. For instance, 74% of the nursing home patients with dementia use antipsychotics, anxiolytics, hypnotics, or sedatives for 83% of the duration of their stay [12], and 31% continue the use of antipsychotics, antidepressants, anxiolytics, hypnotics, anticonvulsants, or anti-dementia drugs throughout a 2-year period [9]. The contradiction of widely prescribed psychotropic drugs despite side effects and limited evidence for (long-term) effectiveness, suggests that psychotropic drugs may be prescribed inappropriately.

Systematic reviews on the effect of education, the involvement of pharmacists, and/or a multidisciplinary team show that these interventions may improve drug prescription in the elderly [13] or in nursing homes specifically [14][15]. For instance, improvements of about 30% in the prescription of drugs in nursing home residents [16][17], and discontinuation or dose reduction of antipsychotics in 61% of patients with dementia [18] have been found. Since the above-mentioned systematic reviews also include high quality studies not showing an effect, the authors suggest to focus in future studies on for example combining methods, multidisciplinary cooperation and direct communication between pharmacist, physician, and nurse, ways to improve the intervention, continuous education, and explicit procedures and routines for medication review. This encouraged us to develop an intervention integrating these elements into a new method of medication review. This medication review will be conducted face-to-face by a multidisciplinary team including not only the physician and pharmacist but

also a member of nursing staff. Further, it will be supported by education on practical, organizational, and medical aspects, continuous evaluation, and will be repeated every six months. It is expected that the education and continuous evaluation offered to all participants gives each of them additional knowledge and structure for proper medication review with a specific emphasis on psychotropic drugs. Furthermore, the participation of nurses, through their daily observations representing the patient, and the face-to-face setting is expected to improve the quality of the review.

The PROPER II study (PRescription Optimization of Psychotropic drugs in Elderly nuRsing home patients with dementia) aims to study the effect of a structured and repeated multidisciplinary medication review supported by education and continuous evaluation on the appropriateness of PDU for treatment of NPS in nursing home patients with dementia. Secondary objectives are to investigate NPS, quality of life, activities of daily living, side effects and adverse events (including cognition, hospitalizations, and mortality).

METHODS/DESIGN
Design and eligibility
The study is a multi-center, cluster randomized controlled, pragmatic trial using parallel groups, with a duration of eighteen months, and four six-monthly assessments. Six nursing homes will participate in the intervention and six will continue care as usual. Randomization will be conducted on the level of nursing homes to prevent contamination bias within the nursing home. The nursing homes will be located throughout the Netherlands, and each will participate with two dementia special care units (DSCUs). In the Netherlands, dementia patients usually reside on DSCUs, and medical care including prescription of psychotropic drugs is provided by an elderly care physician employed by the nursing home [19]. In an investigation preceding the PROPER II study, the observational PROPER I study, the same twelve nursing homes will participate. Nursing homes will be selected based upon their responses on a questionnaire regarding the proportion of patients using psychotropic drugs per individual DSCU. In order to maximize variation in the use of psychotropic drugs in the PROPER II study, those nursing homes, more specifically, those DSCUs with either high or low rates, will be approached for participation. Ideally, six nursing homes with high PDU, and six with low PDU will be included. Since the sample size needed for PROPER II (see below) is lower than for the PROPER I study (Van der Spek et al., submitted), two DSCUs from each participating nursing home will be randomly included in the current study.

In total, 360 patients with a chart diagnosis of dementia will be included, i.e. on average fifteen patients of each of two DSCUs of twelve nursing homes. From DSCUs with more than fifteen patients, a random selection of fifteen patients will be included, regardless of their PDU. For DSCUs with less than fifteen patients, additional DSCUs will participate to retrieve the warranted number of patients per nursing home. Patients who die or are discharged from the DSCU, will be replaced during the study period. Physicians and nurses who are directly involved in the medical treatment and care for the patients will collect the patient data.

This study is a collaboration between the sections for elderly care medicine of three Dutch university Medical Centers and the Dutch Institute for Rational Use of Medicine [20], and is supported by the Dutch association for residential and home care organizations (ActiZ), and the Dutch Health Care Inspectorate.

Intervention
The intervention consists of a structured and repeated multidisciplinary medication review supported by education and continuous evaluation. It consists of three components: 1) preparation and education, followed by a cycle of 2) conduct and 3) evaluation/guidance (figure 1). A local project coordinator will be assigned to ensure appropriate planning and organization of these components. The first component takes place within one month after the baseline assessment of the trial; the second occurs within one month after the first component, or within one month after the evaluation/guidance meeting of the third component; the third component takes place within one month after the six- and twelve-month trial-assessments.

Figure 1. Intervention of the structured and repeated multidisciplinary medication review supported by education and continuous evaluation, consisting of three components.
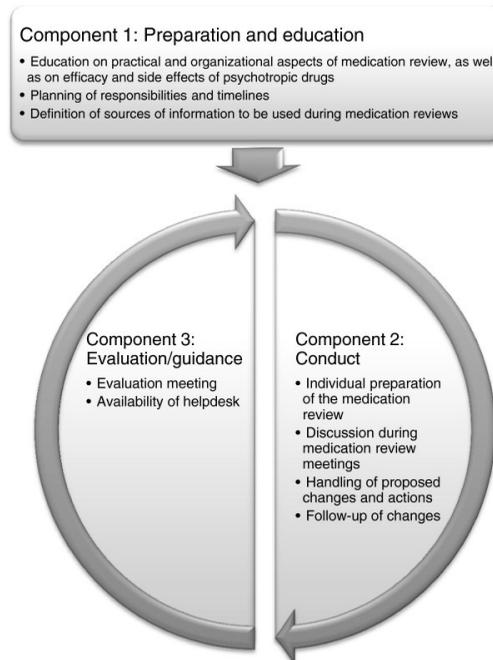
Component 1: Preparation and education
The first component includes all preparations prior to the actual conduct of the medication review. The major part consists of an educational session. The education includes both the practical and organizational aspects of the medication review, as well as training about the efficacy and side effects of psychotropic drugs. It will be provided locally at each intervention nursing home and is to be attended by physicians, pharmacists, and nurses. The content is based upon the Guideline for problem behavior of the Dutch Association of Elderly Care Physicians and Social Geriatricians (Verenso) [21], and the Multidisciplinary guideline Polypharmacy in the elderly [22] including the STRIP method and Dutch versions of the START and STOPP tools [23]. The STRIP is the Systematic Tool to Reduce Inappropriate Prescribing and is a guidance for conducting structured medication reviews, the START is the Screening Tool to Alert doctors to Right Treatment, and the STOPP is the Screening Tool of Older Person's potentially inappropriate Prescriptions. This education will be provided by the Dutch Institute for Rational Use of Medicine (IVM), which is specialized in the distribution of information and solutions for the proper, safe, affordable and effective use of medicine. The education is

developed by the IVM in cooperation with the authors. Next to the education, this component comprises assigning responsibilities of the physicians, pharmacists, and nurses involved, timelines to be followed, and defining those sources of information that each of the participants will use for the medication review.

Component 2: Conduct
The second component includes the actual conduct of the medication review and follow-up per individual patient. The structure is largely based on the STRIP [22]. The conduct of medication reviews per individual patient is a process of preparation, discussion on medication during the medication reviews, execution of the actions proposed, and evaluation of changes. The medication review will be conducted by a team consisting of an (elderly care) physician, pharmacist, and a nurse (assistant). Each of the participants will prepare the medication review. The physician is responsible for collecting medical data of the patient relevant for the discussion, such as type of dementia, comorbidity, and contraindications. The pharmacist is accountable for the actual medication list, knowledge on drug-drug interactions, and dosages. Whereas the STRIP involves the patient in the preparation of the medication review, the patient is in this study represented by the nurse. The nurse is therefore responsible for collecting information about the patient's current behavior and potential PDU-related side effects and adverse events by means of completing a checklist per patient prior to the medication review. The medication review focuses on the appropriate prescription of psychotropic drugs for NPS, but also includes review of other drugs. During the discussion, the team determines whether (psychotropic) drugs must be additionally prescribed, tapered, discontinued, dose-adjusted, or replaced, and whether other actions are needed. These encompass additional diagnostics such as blood checks or electrocardiography, further observations of side effects and adverse events or NPS, referral to a psychologist or to a medical specialist, and use of psychosocial interventions by nursing staff in behavioral management. Proposed changes and actions will be registered and implemented after obtaining consent from the patient's representative. (Non)compliance to the proposed actions is also registered. Further, changes in medication will be followed-up continuously by the physician and nurse.

Component 3: Evaluation/guidance
Evaluation meetings regarding the conduct of the medication reviews will be organized to provide continuous evaluation by guiding and counseling in the process of medication review. These meetings will be provided by the IVM and are to be attended by physician, pharmacist and nurse. Moreover, a help desk provided by the IVM is available for questions.

Outcomes

Primary outcome

The primary outcome is the appropriateness of PDU defined as the proportion of patients with appropriate PDU. Assessment of appropriateness in this study is limited to antiepileptics, antipsychotics, anxiolytics, hypnotics/sedatives, antidepressants, and anti-dementia drugs prescribed for treatment of NPS in dementia, for sleep disturbances, and for delirium. Based on the Medication Appropriateness Index [24], a scale will be developed specifically for those psychotropic drugs used for treatment of NPS in nursing homes. Information will be included from the Guideline for problem behavior of the Dutch Association of Elderly Care Physicians and Social Geriatricians (Verenso) [21], the Guideline for diagnostics and medical treatment of dementia of the Dutch Geriatrics Society [25], the drug database of the Royal Dutch Pharmacists Association [26], and the 'Farmacotherapeutisch Kompas' [27], a reference of drugs available in the Netherlands published by the Dutch Health Care Insurance Board (CVZ).

Secondary outcomes

Secondary outcomes are the overall frequency of PDU, NPS, quality of life, activities of daily living, psychotropic drug side effects and adverse events (including cognition, hospitalizations, and mortality).

The overall frequency of PDU will be collected from the patients' medical files or from (prints of) the electronic pharmacist information system and categorized using the Anatomical Therapeutic Chemical (ATC) classification [28] into the following therapeutic subgroups: antiepileptics (N03A), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), and anti-dementia drugs (N06D).

NPS will be assessed using the Neuropsychiatric Inventory – Questionnaire (NPI-Q), the Cohen-Mansfield Agitation Inventory (CMAI), the Nijmegen Observer-Rated Depression scale (NORD), and the Minimum Data Set Depression Rating Scale (MDS-DRS). The NPI-Q [29] is a brief version of the Neuropsychiatric Inventory, which was developed for measuring NPS in dementia [30]. The NPI-Q consists of twelve items on NPS, each scored for occurrence (yes/no format), severity (three-point Likert scale), and associated caregiver distress of NPS (six-point Likert scale). A validated Dutch version will be used [31]. The CMAI is a questionnaire on 29 agitated behaviors reflecting physical aggression, physically nonaggressive behavior, and verbally agitated behavior. All items regard frequency of behavior using a seven-point Likert scale [32]. The (construct) validity of the Dutch version [33][34] and reliability [35] have been extensively studied. The NORD is a recently developed and

promising Dutch questionnaire on occurrence (yes/no format) of five observable depressive symptoms, for screening of depression in nursing home residents with or without dementia [36]. The MDS-DRS is a seven-item observational instrument consisting of seven items on depression derived from the Minimum Data Set of the Resident Assessment Instrument (MDS-RAI) [37][38]. Each item is scored for frequency on a three-point scale. The Dutch version of this instrument was studied for validity and reliability and considered suitable for research in nursing homes [39].

Quality of life will be assessed using the Qualidem, a 37-item observational instrument consisting of nine subscales for measuring quality of life, each item is scored for frequency on a four-point scale. It was developed for Dutch nursing home patients with dementia and proven reliable and valid [40][41]. In order to allow proper interpretation of the Qualidem scores, the severity of dementia will be assessed using the Global Deterioration Scale, a staging instrument indicating cognitive deterioration in dementia [42]. Additionally, the Revised Index of Social Engagement (RISE) [43] will be assessed. This is an observational instrument with six dichotomous items on social behavior, which is considered to contribute to quality of life. The RISE is a revised version of the Index of Social Engagement [44], and is derived from the MDS-RAI [37][45].

Activities of daily living will be assessed using a questionnaire also derived from the MDS-RAI [46], of which validity and reliability of the Dutch version were established [39]. This scale has been adapted for the Dutch nursing home situation and scoring was simplified, resulting in a scale of twelve items to be scored on a four-point scale for level of independence, and a thirteenth item regarding change compared with the previous month (Joke Smallenburg, personal communication 2011).

Psychotropic drug side effects and adverse events will be assessed by symptoms and disorders related to PDU, cognition, hospitalizations, and mortality. A scale representing common symptoms and disorders related to PDU will be developed for this study, based upon the Udvalg for kliniske undersogelser side effect rating scale (UKU) [47]. Cognition will be assessed using the Severe Impairment Battery-8 [48], a brief version of the Severe Impairment Battery [49]. It was developed as a brief instrument for patients with severe Alzheimer's disease and is sensitive to change over time. The SIB-8 was translated into Dutch for this study. Hospitalizations will be assessed by the number, indication, and duration as reported by the physicians, and mortality will be derived from the patients' medical files.

All assessments will take place at baseline, six months, twelve months and eighteen months. An overview of the outcomes is shown in Table 1.

Table 1. Overview of outcomes, instruments, and assessor at baseline, six, twelve, and eighteen months.

Outcome	Instrument	Assessor
Appropriateness of PDU	To be developed	Researcher
Frequency of PDU	Generic name and ATC code	Researcher
NPS		
NPS	NPI-Q	Nurse
Agitation/aggression	CMAI	Nurse
Depression	NORD	Nurse
Depression	MDS-DRS	Nurse
Quality of life		
Quality of life	Qualidem	Nurse
(For interpretation of Qualidem)	GDS	Physician
Social engagement	RISE	Nurse
Activities of daily living	Instrument derived from MDS-RAI	Nurse
Psychotropic drug side effects and adverse events		
Symptoms and disorders related to PDU	Instrument derived from UKU	Physician
Cognition	SIB-8	Physician/ representative
Hospitalizations	Number, indication, and duration	Physician
Mortality	Occurrence	Researcher

Abbreviations: PDU: psychotropic drug use, ATC: Anatomical Therapeutic Chemical, NPS: neuropsychiatric symptoms, NPI-Q: Neuropsychiatric Inventory – Questionnaire, CMAI: Cohen-Mansfield Agitation Inventory, NORD: Nijmegen Observer-Rated Depression scale, MDS-DRS: Minimum Data Set Depression Rating Scale, GDS: Global Deterioration Scale, RISE: Revised Index of Social Engagement, MDS-RAI: Minimum Data Set Resident Assessment Instrument, UKU: Udvalg for kliniske undersogelser side effect rating scale, SIB-8: Severe Impairment Battery-8.

Baseline characteristics
Other characteristics collected at baseline will be: age, sex, duration of nursing home admission, type of dementia as documented in the patients' files, and comorbidity. Comorbidity will be assessed using a checklist on 25 chronic diseases considered most prevalent in a nursing home population. This checklist is a selection of those International Classification of Primary Care

(ICPC) chronic diseases and comorbidities that are most prevalent in general practice [50], and adapted for the PROPER II study.

Process analysis
Also, a process analysis will be carried out on the actual use of the intervention and the factors determining its implementation, especially regarding facilitators and barriers. In addition, reasons for non-compliance with the intervention and time spent on medication review will be assessed, and the meetings guided by the IVM will be evaluated. Separate checklists for nurses, physicians, pharmacists, as well as for the nursing home's local project coordinator will be used.

Sample size
Assuming an increase in the proportion of patients with appropriate PDU from 60% to 80% in the intervention group and equal randomization to the intervention or control group, a significance level (alpha) of 0.05, a power of 80%, an average cluster size of fifteen patients per DSCU, and an ICC of 0.05 [51], a sample size of 21 clusters is sufficient to detect a statistically significant difference applying Russ Lenth software [52] and calculation methods according to Twisk [53]. Allowing for a DSCU drop-out of ten percent, in total 23 clusters are needed, resulting in the inclusion of two DSCUs in each of twelve nursing homes.

Statistical analysis
Multilevel analysis will be applied to study the change in the proportion of patients with appropriate PDU between baseline and the average at six, twelve, and eighteen months on intervention DSCUs and control DSCUs, after correction of relevant covariates, such as baseline PDU and NPS. The use of a multilevel model will be applied for a number of reasons: patient PDU is hypothesized to be dependent on the prescription policy of the physician and thus to be nested within DSCUs, the longitudinal design and cluster randomization, and the replacement of drop-outs.

Ethics approval
The local Medical Ethics Review Committee 'CMO Regio Arnhem-Nijmegen' rated the study (number 2012/226) and pronounced that the study is in accordance with the applicable rules in the Netherlands concerning the review of research ethics committees and informed consent. Representatives of all selected patients will be approached in writing to inform them about the study and to give them the explicit opportunity to refrain from participation of the patient in the study. The study will be conducted in accordance with the Declaration of Helsinki [54].

CHAPTER 6

DISCUSSION
This protocol presents the design of a cluster randomized controlled trial evaluating the effectiveness of a structured and repeated multidisciplinary medication review supported by education and continuous evaluation to improve appropriate prescription of psychotropic drugs for NPS in nursing home patients with dementia.

The strength of this study's intervention is the multidisciplinary three-component approach of involving professionals who are educated to carry out a structured and repeated medication review. By including not only the pharmacist and physician but also the nurse, the multidisciplinary team is expected to bring optimal knowledge from different perspectives. In this setting, not only medical and pharmaceutical expertise is taken into account, but also insight into the patients' NPS, for which the psychotropic drugs are prescribed. Besides, the nurse has close contact with the representative of the patient, which further allows input on wishes regarding treatment or acceptation of NPS for the individual patient to be included in the medication review. Moreover, this study is a broad collaboration between several Dutch parties. Aside from the sections for elderly care medicine of three Dutch university Medical Centers, which have close connections with numerous nursing homes, the Dutch Institute for Rational Use of Medicine, the Dutch association for residential and home care organizations (ActiZ), and the Dutch Health Care Inspectorate are actively involved in this project. This has not only contributed to the design of the study and structure of the intervention, but will also facilitate the knowledge transfer of the results to daily practice after completion of the study. In case effectiveness of this three-component intervention is shown, this medication review method will be used on a broader scale to increase awareness of physicians, pharmacists and nurses of proper psychotropic drug use.

The study may have some limitations. Firstly, the involvement of a pharmacist for medication review is currently starting to become part of usual care, also in the control nursing homes. However, these medication reviews are most likely not introduced in a similar education-based, structured, and multidisciplinary fashion. Secondly, the turn-over of pharmacists, physicians, and/or nurses will affect the knowledge regarding the proposed conduct of the medication reviews, in case new staff did not attend the education sessions. However, due to the pragmatic design, the study will have a large external validity and it is expected that a potential effect is at least not overestimated.

Concluding, in the PROPER II study we target to improve the quality of pharmacological treatment of NPS of nursing home patients with dementia, by implementing a sound intervention of a structured and repeated multidisciplinary medication review supported by education and continuous evaluation.

COMPETING INTERESTS
The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS
SZ designed the study, DG and MS co-designed, and RK assisted in designing the study. The Dutch Institute for Rational Use of Medicine in cooperation with the authors designed the intervention. CS wrote the paper, and MS, DG, MN, RW, KS, SZ, and RK co-wrote the paper. All authors read and approved the manuscript.

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CHAPTER 6

The effect of biannual medication reviews on the appropriateness of psychotropic drug use for neuropsychiatric symptoms in patients with dementia: a randomised controlled trial
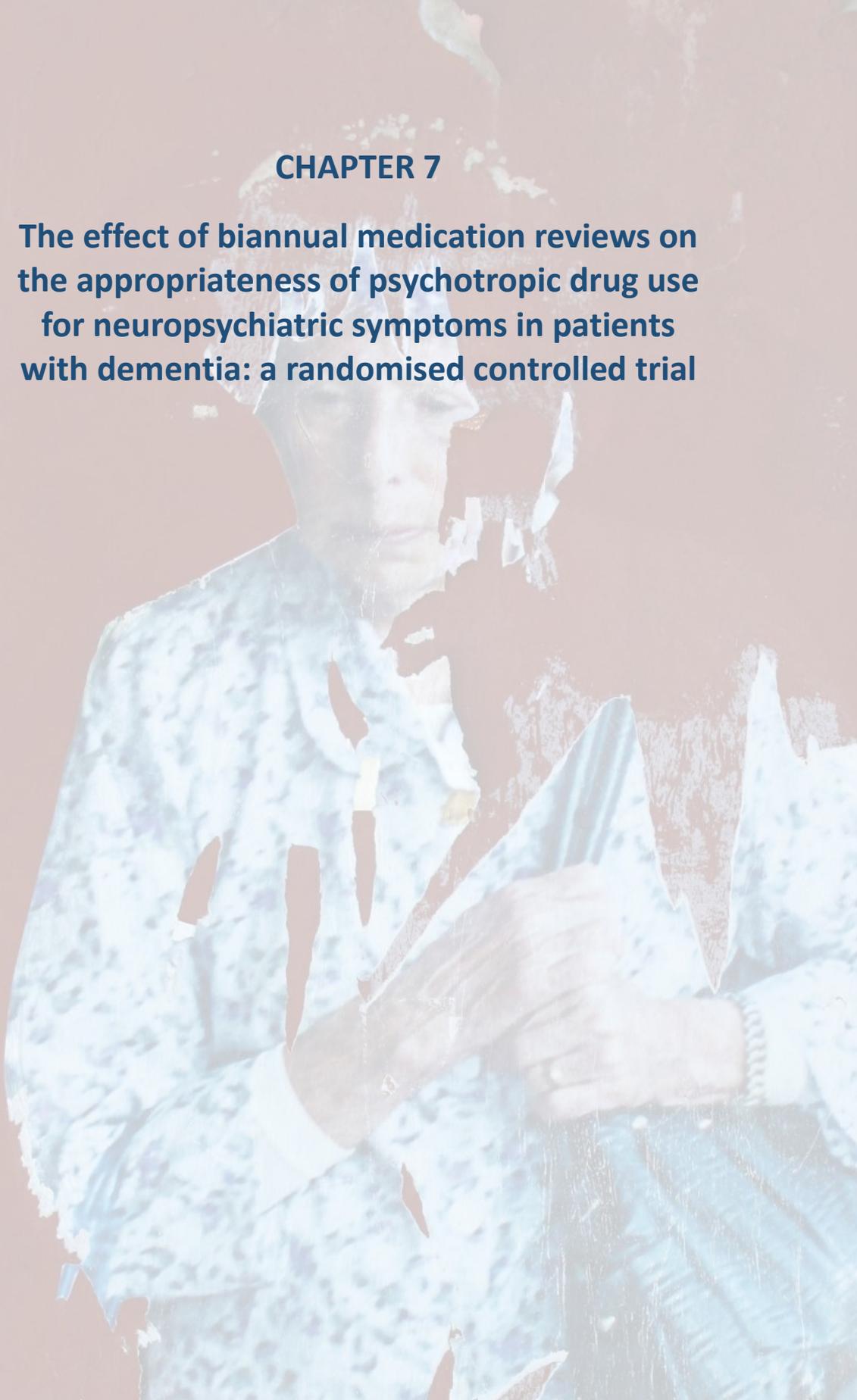
CHAPTER 7

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ABSTRACT
Introduction
We studied the efficacy of biannual structured medication reviews to improve
the appropriateness of psychotropic drug (PD) prescriptions for
neuropsychiatric symptoms (NPS) in nursing home patients with dementia.

Trail, study design and setting
The intervention encompassed a structured multidisciplinary medication
review by physician, pharmacist and nurse. During this eighteen-month study,
the patient's medical files were assessed every six months.
The primary outcome was the appropriateness of PD prescriptions defined by
the Appropriate Psychotropic Drug use In Dementia (APID) index sum score,
lower scores indicating more appropriate use.

Results
At baseline, 380 patients were included, of which 222 were randomised to the
intervention group. Compared to the control group, the APID index sum score
in the intervention group improved significantly for all PD prescriptions (-5.28,
p = 0.005).

Conclusion
We advise the implementation of a structured, repeated medication review
with the essential roles of pharmacist, physician and nurse, into daily practice.

CHAPTER 7

INTRODUCTION

Many nursing home residents with dementia have neuropsychiatric symptoms (NPS) which are frequently treated with psychotropic drugs , e.g. antipsychotics, antidepressants, anxiolytics and hypnotics [1][2]. However, there is substantial evidence for the existence of risks, side effects and long-term inefficacy of psychotropic drugs [3][4], which is why the guidelines recommend the restricted and short-term use [5]. Nevertheless, there is some literature available reporting that psychotropic drugs are being used for excessively long periods [6][7][8], simultaneously [1], and without a proper indication [9][10]. These findings suggest inappropriate psychotropic drug prescriptions, thereby emphasising the need for optimisation strategies.

Systematic reviews [11][12][13] as well as individual studies [11][14][15] in different settings, i.e. hospital [11][14] and nursing homes [15], show that a multidisciplinary medication review with the involvement of a pharmacist [12] and the additional presence of a nurse [12] has beneficial effects on appropriate drug prescription. Although there is evidence to suggest that a medication review may result in the improved appropriateness of drug prescription in general [16], studies on psychotropic drug prescription are unclear [15].

In the current study, we aim to study the impact of a structured repeated multidisciplinary medication review on the appropriateness of psychotropic drug prescriptions. Recently, we developed the Appropriate Psychotropic drug use In Dementia index (APID index) [17]. This instrument is based on the Medication Appropriateness Index (MAI) [18] and makes it possible to specifically measure the appropriateness of psychotropic drug prescription for NPS in dementia on seven different domains, i.e. indication, evaluation, dosage, drug-drug interactions, drug-disease interactions, duplications and therapy duration.

Based on an earlier study [19], we hypothesise that the appropriateness-domains indication, evaluation and therapy duration contribute the most to the inappropriateness of psychotropic drug prescription [19] and will improve the most by this intervention.

METHODS
Trial design

The PROPER II study (PRescription Optimisation of Psychotropic drugs in Elderly nuRsing home patients with dementia), investigated the effects of a newly developed medication review intervention in a multi-centre, cluster randomised controlled pragmatic trial using parallel groups [20]. The intervention group performed a structured, repeated (psychotropic) drug review, and the control group continued care as usual [20]. The study was conducted for eighteen months, with four biannual assessments.

Sample size
Allowing for a cluster drop-out of ten per cent, in total 23 clusters (i.e. dementia special care units), with 15 patients on average, would provide >80% power to detect an absolute difference of 20% in the appropriateness of psychotropic drug prescriptions, as detailed in the study design paper [20].

Recruitment and randomisation
The nursing homes recruited for PROPER II [20] were those already recruited for PROPER I, a cross-sectional mixed methods study that aimed to investigate (the appropriateness of) psychotropic drug prescriptions and its associations. For PROPER I twenty-seven long-term care organisations were contacted in order to include the necessary 13 nursing homes, located throughout the Netherlands. In the Netherlands, nursing homes are part of long-term care organisations and have dementia special care units that differ in size between 5 and 30 patients. Usually, individual patients have one registered nurse and an elderly care physician assigned that is primarily responsible for their care [21]. A random selection of the dementia special care units that participated in PROPER I [22] was included in PROPER II. On average, 30 patients per location were included, residing in two or more dementia special care units depending on the size of the units. Randomisation was blinded, i.e. computer-generated, and conducted on the level of nursing homes to prevent contamination bias within the nursing home. Seven nursing homes participated in the intervention and six continued care as usual.

Patient involvement and ethics
Patients were not directly involved in the study, information about psychotropic drug prescriptions were obtained from medical records. Physicians and nurses who were directly involved in the medical treatment and care for the patients collected data about the patients [20]. The inclusion criteria of PROPER II were (1) a chart diagnosis of dementia, (2) not terminally ill and (3) admitted for long stay. Patients who died or moved from the dementia special care unit were replaced by newly admitted patients on that units during the study. Representatives of all selected patients were approached in writing to inform them about the study and to give them the explicit opportunity to refrain from the participation of the patient in the study.
    The local Medical Ethics Review Committee 'CMO Regio Arnhem-Nijmegen' judged/reviewed the study (number 2012/226) and pronounced that the study is carried out in accordance with the applicable rules in the Netherlands concerning the review of research ethics committees and informed consent.

PROPER II Intervention

A newly developed method of structured and repeated multidisciplinary medication review was introduced for nursing home patients with dementia with the focus on psychotropic drugs prescribed for NPS. This medication review was carried out by the nursing homes own multidisciplinary team, i.e. the responsible physician, the pharmacist and the nurse [20].

The intervention consisted of three components:

Component 1) a preparation and education phase that included instruction about the practical and organisational aspects of the medication review and a training about the efficacy and side effects of psychotropic drugs, which were to be attended by physicians, pharmacists and nurses. The education was provided by the Dutch Institute for Rational Use of Medicine (IVM) and emphasised the adherence to the Guideline for problem behaviour of the Dutch Association of Elderly Care Physicians and Social Geriatricians (Verenso) [5], the Multidisciplinary guideline Polypharmacy in the elder [23] (including the Systematic Tool to Reduce Inappropriate Prescribing (STRIP), the Screening Tool to Alert doctors to Right Treatment (START) and the Screening Tool of Older Person's potentially inappropriate Prescriptions (STOPP) [14]).

Component 2) the actual medication review, which was conducted at 0-, 6- and 12-months by the multidisciplinary team. This team prepared the medication review with discipline-specific information, including data of the patient, pharmaceutical information and information about the patient's current behaviour (obtained by nurses using a checklist) and potential psychotropic drug use-related side effects (obtained by physicians using a checklist). The medication review focused on the appropriate prescription of psychotropic drugs, but also included the review of other drugs. In case of multidisciplinary team agreement, medication adjustments were introduced after having consulted the patients' representatives.

Component 3) an evaluation phase prior to the reviews at 6 and 12 months. Meetings with all stakeholders, i.e. physician, pharmacist and nurse, were organised in order to evaluate the intervention.

In each nursing home, an intervention coordinator was assigned to ensure the planning and organisation of these components. The intervention is described extensively elsewhere [20].

Assessments and outcomes

Assessment of appropriateness in this study was limited to antipsychotics, anxiolytics, hypnotics/sedatives, antidepressants, antiepileptics and anti-dementia drugs.

The appropriateness of psychotropic drug prescriptions was assessed using the Appropriate Psychotropic drug use In Dementia (APID) index [17]. The APID index was specifically developed for clinical studies evaluating the appropriateness of psychotropic drug prescriptions for NPS in patients with dementia in nursing homes. Therefore, psychotropic drugs that had a clear indication for other psychiatric disorders in the medical record (apart from dementia or sleeping disorder or delirium) were excluded from scoring [17]. Recommendations from national (Dutch) and international drug formularies were applied in order to score information about individual psychotropic drugs. The response categories of the seven domains were 0 (appropriate), 1 (marginally appropriate) and 2 (inappropriate); the domains were weighted and incorporated into a sum score. The sum score ranges from 0 (fully appropriate) to 102.8 (fully inappropriate) on individual psychotropic drugs [17].

The primary outcome was the level of appropriateness of psychotropic drug use as defined by the Appropriate Psychotropic Drug use In Dementia (APID) index sum score.

Secondary outcomes were the appropriateness of indication, evaluation and therapy duration, defined by the APID index subscores on these domains [17]. The theoretical weighted score-ranges for these domains of appropriateness are as follows: indication 0-18.8, evaluation 0-19.2 and therapy duration 0-12.2.

The analyses of all psychotropic drug prescriptions combined and per psychotropic drug group were performed. Psychotropic drugs were grouped using the Anatomical Therapeutic Chemical classification (ATC) [23]. Antidepressants, as well as anti-dementia drugs, do not have the maximum therapy duration according to Dutch drug formularies [5]. Therefore, these psychotropic drugs cannot be scored as inappropriate for therapy duration.

Baseline characteristics

Other characteristics that were collected at baseline were number of dementia special care units, age, sex, duration of nursing home admission and type of dementia as documented in the patients' files. The type of dementia was categorised in Alzheimer Dementia (AD), Vascular Dementia (VaD), Mixed AD/VaD and other dementia.

Statistical analysis

Descriptive statistics were used to examine the baseline characteristics. When more than a 10% difference between the intervention- and control group was observed, an independent samples t-test was performed to test the effect of this parameter on the primary outcome (APID index sum score).

At baseline and after 6, 12 and 18 months, the mean APID index sum scores, the mean APID index subscores for indication, evaluation and therapy duration, including the standard deviations and 95% confidence intervals were calculated.

A linear mixed model for repeated measurements of the outcome averaged at dementia special care unit (cluster) levels was used with time and treatment (1 in the intervention group at 6, 12 and 18 months and 0 otherwise) as fixed effects (which is equivalent to a time x treatment interaction assuming no systematic difference between groups at baseline due to the randomisation) and dementia special care unit as random effect. Residuals of the mixed model were checked for trends indicating non-normal distribution. The effect in our trial was thus the average effect of the intervention versus control, averaged over month 6, 12, and 18.

First, analyses on all prescriptions taken together were performed, followed by analyses per psychotropic drug group.

RESULTS

Recruitment and flowchart

Eleven of the 27 long-term care organisations that were contacted decided not to take part because of a) lack of time or insufficient staffing (physician or nurse) to carry out the project (N=5); b) an ongoing reorganisation (N=3); c) involvement in another (research) project (N=2); and d) unit managers who were unwilling to participate (N=1). The study was conducted from September 2012 to July 2014. The 12 long-term care organisations that completed the study were equally distributed over various rural and urban parts of the Netherlands.

The flowchart (Figure 1) provides an overview of the participating units and patients during the study.

Figure 1. Study flowchart for the outcome analysis, please see Appendix C.

Baseline characteristics

Table 1. Baseline characteristics.

Baseline Characteristics of Nursing Home patients	Intervention (n=222)	Control (n= 158)
Number of dementia special care units (clusters)	15	16
Mean age (years), [SD] (range)	84 [7.4] (55-99)	83 [7.3] (55-99)
Sex, female N (%)	173 (77.9%)	114 (72.2%)
Length of stay at dementia special care unit (months), [SD] (range)	25 [21.8] (0-118)	24.4 [21.7] (0-114)
Number of psychotropic drugs used in total sample at baseline	114 (51.4%)	88 (55.7%)
Diagnosis of dementia, N (%)		
Alzheimer's dementia	90 (40.5%)	37 (23.4%)
Vascular dementia	27 (12.2%)	29 (18.4%)
Mixed Alzheimer's/vascular dementia	22 (9.9%)	19 (12.0%)
Other dementia	83 (37.4%)	73 (46.2%)

Marginal baseline differences (see Table 1) were found between the intervention group and the control group for sex (77.9% and 72.2%) and number of psychotropic drugs used (51.4% and 55.7%). Although there was a difference between the intervention group and the control group in the prevalence of types of dementia, an independent sample t-test of the mean APID index sum score per patient at baseline revealed no significant differences between dementia types (AD, $p = 0.264$; VaD, $p = 0.696$; mixed AD/VaD, $p = 0.200$; other dementia, $p = 0.811$).

Table 2. Observed APID index sum score means of all psychotropic drug prescriptions at baseline, 6, 12 and 18 months.

Outcome	Theoretical range		Observed Mean APID index sum score (CI)			
			Baseline PDs n=329 Clusters n=31	After 6 months PDs n=306 Clusters n=29	After 12 months PDs n=278 Clusters n=28	After 18 months PDs n=272 Clusters n=29
APID index sum score	0-120.8	Intervention	29.0 (CI= 26.1: 32.0)	21.1 (CI= 17.6: 24.4)	19.1 (CI=14.4: 23.7)	19.1 (CI= 16.6: 21.6)
		Control		29.2 (CI= 24.0: 34.4)	28.5 CI 24.1: 32.9)	28.2 (CI 22.7: 33.8)
Indication subscore	0-18.8	Intervention	11.4 (CI= 10.0: 12.9)	8.4 (CI= 6.5: 10.3)	8.0 (CI= 5.8: 10.2)	7.4 (CI= 5.8: 9.0)
		Control		11.5 (CI= 8.7: 14.4)	11.9 (CI= 8.6: 15.1)	11.1 (CI= 8.1: 14.0)
Evaluation subscore	0-19.2	Intervention	8.0 (CI= 6.4: 9.7)	3.6 (CI=1.9: 5.3)	2.8 (CI= 1.2: 4.3)	2.0 (CI= 0.8: 3.3)
		Control		8.1 (CI=5.1: 11.1)	8.4 (CI= 5.9: 10.9)	8.5 (CI= 5.0: 12.0)
Therapy duration subscore	0-12.2	Intervention	5.8 (CI= 4.9: 6.8)	4.9 (CI= 3.4: 6.3)	5.1 (CI= 3.8: 6.3)	5.7 (CI= 4.7: 6.8)
		Control		7.0 (CI= 5.5: 8.6)	6.0 (CI= 4.2: 7.8)	6.3 (CI= 4.4: 8.1)

APID= Appropriate Psychotropic drug use In Dementia, PDs= psychotropic drugs, CI= 95% confidence interval

Outcomes measures
The average improvement over 6, 12, and 18 months of the mean APID index sum score for all psychotropic drug prescriptions together over time (as shown in Table 2) was significantly greater (as shown in Table 3) in the intervention group than the control group (-5.28, p = 0.005). This was also the case for the evaluation subscore (-2.26, p = 0.008). The mean APID index subscore for therapy duration declined significantly less in the intervention group (-1.65, p = 0.020). The indication subscore (-1.91, p=0.150) did not show differences (Table 3).

Table 3. Effect of structural medication reviews on the APID index sum score, indication score, evaluation score and therapy duration score of psychotropic drug prescriptions.[1]

Parameter	n at baseline/ number of clusters	Sum score TR 0-102.8	Indication TR 0-18.8	Evaluation TR 0-19.2	Therapy duration TR 0-12.2
APID index all prescriptions	329/ 31	**-5.28 (CI = -8.87: -1.69 and p= 0.005*)**	-1.91 (CI= -4.55: -0.75 and p=0.150)	**-2.26 (CI= -3.86: -0.65 and p=0.008*)**	**-1.65 (CI= -3.03: -0.28 and p=0.020*)**
Specified per psychotropic drug group					
APID index antipsychotics	85/ 31	-6.64 (CI= -13.51: -0.22 and p=0.057)	-0.68 (CI= -3.24: 1.88 and p=0.585)	-0.07 (CI= -3.78: 3.65 and p=0.970)	**-1.44 (CI= -2.83: -0.05 and p=0.043*)**
APID index anxiolytics	54/ 31	**-10.85 (CI= -17.17: -4.53 and p=0.002*)**	**-10.09 (CI= -14.16: -6.03 and p<0.001*)**	-2.39 (CI= -5.47: 0.69 and p=0.123)	-0.31 (CI= -1.03: 0.41 and p=0.379)
APID index hypnotics/sedatives	49/ 31	-4.07 (CI= -9.53: 1.39 and p=0.135)	0.62 (CI= -3.40: 4.64 and p=0.749)	**-7.49 (CI= -10.83: -4.15 and p<0.001*)**	**-2.94 (CI= -4.73: -1.16 and p=0.003*)**
APID index antidepressants	90/ 31	**-5.33 (CI= -10.11: -0.56 and p=0.030*)**	**-2.94 (CI= -5.72: -0.16 and p=0.039*)**	**-5.31 (CI= -7.72: -2.89 and p<0.001*)**	n.a.
APID index anti-dementia drugs	38/ 31	3.77 (CI= -6.09: 13.64 and p=0.430)	-2.83 (CI= -9.91: 4.25 and p=0.411)	**4.27 (CI= 0.36: 8.18 and p=0.038*)**	n.a.

*= significant influence on regression p<0.05, CI= 95% confidence interval, n.a. = not applicable, TR = theoretical range.
[1]Analyses were performed on cluster-level. Analyses on antiepileptics were excluded, considering the small sample size (n=13 at baseline). Adjacent small dementia special care units sharing staff and corridors that had few participating patients, i.e. ≤ 3 patients participating on each unit at one or more of the measurement points, were grouped. This was the case for three different nursing homes: two, three, five and five dementia special care units, respectively, with shared staff and corridors were grouped into larger clusters encompassing at least nine patients participating at baseline, after 6, 12 or 18 months.

Outcomes specified per psychotropic drug group
More specifically, the APID index sum score and indication subscore for anxiolytics (-10.85, p = 0.002 and -10.09, p = 0.000) and antidepressants (-5.33, p = 0.030 and 2.94, p = 0.039) showed a statistically significant greater improvement in the intervention group compared to the control group. For hypnotics/sedatives (-7.49, p < 0.001) and antidepressants (-5.31, p < 0.001) the evaluation subscore showed a significantly greater improvement in the intervention group compared to the control group, and a negative effect was found on the evaluation subscore for anti-dementia drugs (4.27, p = 0.038). Therapy duration subscore showed a significantly greater improvement in the intervention group compared to the control group for antipsychotics (-1.44, p = 0.043) and hypnotics/sedatives (-2.94, p = 0.003) (Table 3).

DISCUSSION
Main findings
This innovative study demonstrated that the appropriateness of psychotropic drug prescriptions for NPS improved by structurally reviewing the prescriptions of nursing home patients with dementia every six months. Regarding all psychotropic prescriptions combined, overall appropriateness improved; on the level of domains, the evaluation and the therapy duration improved.

In addition, in the control group, the overall appropriateness, indications and evaluations also improved, which could be due to the current societal attention for psychotropic drug prescriptions in nursing homes [25] and increased awareness as a result from participation in this study.

To summarise, a biannual multidisciplinary review approach and attention for psychotropic drug prescriptions for NPS in dementia improves the efficacy of the evaluation and therapy duration, but changing to indications that are more appropriate may need a different approach and more attention on this domain during medication reviews.

Strengths and limitations
One of the strengths of our study was its multidisciplinary team approach; the presence of the nurses, which makes it possible to have more detailed information on the patients' present condition in terms of NPS, in combination with the side effects associated with psychotropic drug use, monitored by physicians, and pharmaceutical information, provided by pharmacists. Furthermore, we used a newly developed instrument to assess inappropriate psychotropic drug use rated by researchers, independent from the opinion of the treating physician.

A limitation is the low participation rate in some dementia special care units, resulting in a few small clusters. Additionally, the overall sample size of some psychotropic drug groups was small; therefore, group specific reports should be interpreted carefully. Another limitation may be that the outcome measurement, the APID index, is partly based on Dutch drug formularies, implying for instance that some psychotropic drugs cannot be scored as inappropriate for therapy duration. Further, it uses patient records. As a result, the score may be affected by suboptimal recordkeeping. However, good recordkeeping can be considered as an indispensable prerequisite for judging the appropriateness of prescription; physicians need good recordkeeping to evaluate the psychotropic drug prescriptions [17].

Clinical implications

The clinical use of off-label prescriptions is widespread [26]; many different psychotropic drugs are prescribed to individual patients with similar NPS [19][27]. Psychotropic drug prescriptions for NPS in dementia were rated as appropriate when guidelines recommended these specific prescriptions for a NPS, but even when there is maximum guideline adherence, there still is limited evidence for the efficacy of treatment [25] and, therefore, psychotropic drugs should be regularly evaluated. Additionally, antipsychotics, anxiolytics and hypnotics/sedatives are used too long [8][19].

Improvement of guideline recommended indications, appropriate evaluations of effects and therapy duration, could be facilitated with a psychotropic drug prescription monitor, based on the APID index, that is suitable for daily practice. This instrument could increase the awareness of inappropriate prescriptions of psychotropic drugs for NPS and, consequently, facilitate the implementation of the medication review.

This study was performed in the Netherlands with trained elderly care physicians as the responsible physician, the pharmacist and the nurse. The structure of a medication review service may differ worldwide, however, since the appropriateness of psychotropic drug prescriptions is a worldwide challenge and similar interventions (including pharmacists and physicians) on reducing (the appropriateness of) psychotropic drug use were performed in other countries [14][28][29][30], the results may very well be generalisable to other countries.

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CHAPTER 7

CHAPTER 8

GENERAL DISCUSSION

CHAPTER 8

INTRODUCTION

There is an ever increasing interest in reducing psychotropic drug (PD) use for neuropsychiatric symptoms (NPS) in institutionalized patients with dementia. While initiatives focus on reducing the frequency (prevalence), the appropriateness of these prescriptions has received less attention. However, that could be key for beneficial PD use, consequently improving its effectiveness and reducing side effects.

The first part of this thesis (PROPER I) focuses on the development of the APID, an index to objectify the construct appropriateness of PD use for NPS in dementia, measure the current appropriateness with this index and determine factors associated with appropriateness.

The second part of this thesis (PROPER II) focuses, based on the abovementioned exploration of appropriateness, on the improvement of potentially inappropriate prescriptions.

Prior to discussing the performed studies and their results, a summary of the findings is given according to the thesis' research questions on PD prescriptions for NPS among nursing home patients with dementia:

1. How to measure appropriateness of psychotropic drug prescriptions?
2. How appropriate are psychotropic drug prescriptions for neuropsychiatric symptoms?
3. What factors are associated with the appropriateness of psychotropic drug prescriptions?
4. How to improve the appropriateness of PD prescriptions?

Second, the methodological considerations, the clinical implications, the societal impact and recommendations for future research are discussed.

SUMMARY OF FINDINGS
How to measure appropriateness of psychotropic drug prescriptions?
Chapter 3 describes the development of an index that is suited for clinical studies evaluating appropriateness of PD prescriptions for NPS in nursing homes patients with dementia and to test its reliability and validity; the design is described in chapter 2.

The Medication Appropriateness index (MAI) [1] is an index that was developed to measure appropriateness of drug use in general, but it is not specifically aimed at assessing appropriateness of PD prescriptions for NPS in dementia. In addition, the MAI does not fit specific drug utilization formularies, which is preferable when drug utilization reviews are applied.

Therefore, an index was developed, derived from the items of the MAI, that is specifically suited for clinical studies evaluating the appropriateness of PD prescriptions for NPS in nursing homes patients with dementia. An expert panel reviewed the MAI items; five existing MAI items were found suitable, the MAI item 'indication' was adjusted, a new item 'evaluation' was added, and scoring rules were based on guideline recommendations, to create the Appropriate Psychotropic drug use In Dementia (APID) index. A second independent expert panel determined that all items contributed to the construct 'appropriateness'. This resulted in an index that encompasses seven (different) domains of appropriateness, i.e. indication, evaluation, dosage, drug-drug interactions, drug-disease interactions, duplications and therapy duration. An interrater reliability study was conducted, and a summated index score, based on weighted item scores, was developed to enhance the use in clinical studies. The APID index score is calculated using information about individual PDs from patients' medical records. Construct validity was explored using a representative sample of 560 medical records. Information from PD prescription guidelines and the summary of product characteristics from the medication evaluation board [2], which was retrieved by Dutch databases for drug prescriptions, was integrated into the seven items of the APID index for each PD [3][4].

The results of this study showed that the APID index is reliable and valid for measuring the appropriateness of PD prescriptions for NPS in nursing home patients with dementia in clinical studies.

How appropriate are psychotropic drug prescriptions for neuropsychiatric symptoms?

Chapter 4 describes the exploration of the status of the appropriateness of PD prescriptions for NPS in nursing home patients with dementia; the design is described in chapter 2.

A cross-sectional study among 559 patients with dementia residing on Dementia Special Care Units (DSCUs) in Dutch nursing homes was conducted. Appropriateness of PD prescription was assessed using the APID index. A total of 578 PDs were used for NPS by 60% of the patients. Of the seven APID index' items it appeared that indication, evaluation and therapy duration contributed the most to inappropriate use. The minority of the PDs, only 10%, scored fully appropriate according to the APID index sum score, 36% scored fully appropriate for 'indication', 46% scored fully appropriate for 'evaluation', and 58% scored fully appropriate for 'therapy duration'. Antidepressants were used the most appropriately, and antiepileptics the most inappropriately. Appropriateness was not associated with the number of PDs used per patient, the percentage of use on the DSCUs, nor the percentage of prescription of the

individual physicians (i.e. the number of their patients with one or more PD prescriptions).

The results imply that there is room for improvement of the PD prescriptions for NPS in patients with dementia and that it should be optimized with a clinical focus on the appropriateness of indication, evaluation, and therapy duration, which guided us to focus on these domains in the exploration of the appropriateness of different individual and groups of PDs.

What factors are associated with the appropriateness of psychotropic drug prescriptions?
Chapter 5 describes the cross-sectional study on patient and non-patient factors associated with (in) appropriate PD prescription as measured with the APID index sum score; the design of a conceptual framework about potential associations is described in chapter 2.

  The sample consisted of 559 patients that used 147 antipsychotics, 167 antidepressants, 85 anxiolytics and 76 hypnotics/sedatives. Various measurements were carried out for patient and non-patient factors (e.g. NPS, NPS related nurses' stress, attitude to dementia care of caregivers, physicians' experience, time available per patient) using questionnaires, assessment instruments and patient records.

  Linear multilevel regression analysis was used to identify factors that are associated with APID index sum scores. Analyses were performed for four groups of PDs separately, i.e. antipsychotics, antidepressants, anxiolytics and hypnotics/sedatives. It was found that older age and more severe aggression, agitation, apathy and depression were associated with more appropriate prescriptions.

  Less appropriate prescriptions were found to be associated with more severe anxiety and non-Alzheimer's dementias. Several non-patient related factors were also associated with less appropriate PD prescriptions (more patients per physician and higher nurses' workload) and some of these findings were counter-intuitive (more physician time available per patient, more years of experience of the physician).

How to improve the appropriateness of PD prescriptions?
Chapter 7 describes the efficacy of a multi-centre cluster randomised controlled trial on implementing biannual structured medication reviews to improve the appropriateness of PD prescriptions for NPS in nursing home patients with dementia. The design is described in chapter 6.

The PROPER II intervention consists of a structured and repeated multidisciplinary medication review supported by education and biannual evaluation. It was conducted by pharmacists, physicians, and nurses and consisted of three components: 1) preparation and education, 2) conduct, and 3) evaluation and guidance. The primary outcome was the appropriateness of PD prescriptions defined by the APID index sum score, lower scores indicating more appropriate use.

During this eighteen-month randomised controlled trial, the patients' medical files were assessed every six months. At baseline, 380 patients were included, of which 222 were randomised to the intervention group. Compared to the control group, the APID index sum score in the intervention group improved significantly for all PD prescriptions combined. This was also the case for the subscore 'evaluation' and the subscore 'therapy duration'. The subscore 'indication' did not show a significant difference.

More specifically, per PD group, the APID index sum score and indication subscore for anxiolytics and antidepressants showed a statistically significant greater improvement in the intervention group compared to the control group. For hypnotics/sedatives, antidepressants and anti-dementia drugs the evaluation subscore improved significantly in the intervention group compared to the control group. The therapy duration subscore also improved significantly in the intervention group compared to the control group for antipsychotics and hypnotics/sedatives.

Based on these results, the implementation of a structured repeated medication review for PD prescriptions into daily practice is recommended, with the essential roles of pharmacist, physician and nurse.

METHODOLOGICAL CONSIDERATIONS

Study population/response rate

For PROPER I 13 long-term care organisations (LTCOs) were recruited, located throughout the Netherlands. In the Netherlands, nursing homes are part of LTCOs and have Dementia Special Care Units (DSCUs) that differ in size between 5 and 30 patients. A random selection of the DSCUs that participated in PROPER I (see chapter 2) was included in PROPER II (see chapter 6), which resulted in the absence of selection bias.

The PROPER I sample consisted of 559 patients, 338 used one or more PDs, living in 44 different DSCUs of 12 Dutch LTCOs. Only few (<10) objected to participation. The mean age was 84 years (range 62-100) and 73.8% was female. These findings were similar to the results found in other studies [9][5][6]. Therefore, the sample was considered as a good representation of

Dutch long-term care patients residing on DSCUs; the sample had good external validity.

The PROPER II sample at baseline consisted of 222 patients residing on 15 DSCUs in the intervention group and 158 patients residing on 16 DSCUs in the control group. Again only few (<10) objected to participation. Baseline differences were found between the intervention group and the control group for sex (77.9% and 72.2%), number of PDs used (51.4% and 55.7%) and percentage of Alzheimer's dementia (40.5% and 23.4%). Although differences between the intervention group and the control group in the prevalence were found, independent sample t-testing of the mean APID index sum score between the groups at baseline revealed no significant differences. Moreover the mean APID index sum score was found independent from prevalence (chapter 4), therefore, we did not correct for this in the final analyses.

The participation rate in some DSCUs was limited, although sample size calculation was performed prior to recruitment for PROPER II (chapter 6) and new patients were recruited during the study period to compensate for patients who died or were discharged from the DSCU. The limited participation rate resulted in a few small clusters during the study period, see chapter 7. Additionally, the sample size of some PD groups was small; therefore, PD group specific reports should be interpreted carefully. Nevertheless, the samples were sufficient to detect significant differences.

Study design
In this thesis the status of the appropriateness of PD prescriptions for NPS in Dutch patients with dementia residing in LTCOs was explored by using the APID index, see chapter 4. Prior to that measurement, the major part participated in the development and validity study of the APID index. However, uncertainty exists about the generalisability of the status of the appropriateness to other samples, which could be considered as a limitation of the study design. Therefore, the APID index should be used on other samples to test the external validity of the results from the study on the status of the appropriateness (chapter 4).

To our knowledge chapter 5 describes the first study that was performed to identify potential associations with the appropriateness of PD prescription for NPS in patients with dementia specifically. Primarily patient factors were associated with the appropriateness of PD prescriptions, which implies that physicians should pay more attention to the appropriateness when NPS are less severe. The search for associations is complex. Different factors have been mentioned in the literature, e.g. the presence of behavioural symptoms and female sex have been found to be associated with more appropriate indications of benzodiazepines[7]. We developed a conceptual framework of factors associated with the appropriateness of PD

prescriptions (chapter 2), we assumed that appropriate prescription of PDs has a similar multifactorial nature as it has for the frequency of PD prescription [8]. The statistical limitations in searching for the most important of these associations have once again been confirmed in this thesis; there are too many potential associations even for reasonably large samples [9]. The assumed multifactorial nature of PD prescriptions in dementia care resulted in that we collected too many factors, see chapter 2, whereas including all possibly relevant factors could lead to an overfit of statistical models[9]. Therefore, it can be considered as a limitation of the PROPER I study design and made the authors decide to make a selection of factors potentially associated with appropriate PD prescription. This selection was based on the existing knowledge about the factors associated with PD prescriptions and the clinical expertise of the authors. Due to this selection, relevant but still unknown factors might have been missed.

The construct 'appropriateness'
In this thesis the development and validation of the first medication index specified to measure the appropriateness of PD prescriptions for NPS in nursing home residents with dementia was described. All seven newly developed APID index items had good content validity and no multicollinearity was found between the items. However, considering that the construct 'specified to measure the appropriateness of PD prescription for NPS in dementia' was newly developed, there is no gold standard to validate the index as a good measure for this construct. The issues faced with this new construct are discussed here:

Literature on appropriateness indicators [10][11][12] shows that the items 'indication', 'evaluation' and 'duration of therapy' have a large contribution to inappropriateness of PD prescriptions. These results are in line with results of a multi-intervention study on all drugs used by elderly patients which found that the items indication, duration and expense where most inappropriate using the MAI [13], and also with our second expert panel's highest mean weighting for the items 'indication' and 'evaluation'.

The abovementioned findings are consistent with the results of chapter 4, which also found that 'indication', 'evaluation' and 'therapy duration' contributed the most to the mean summated index score, thus the overall inappropriateness. In relation to this issue, one might argue that especially the items indication and evaluation were bound to contribute more to the overall inappropriateness considering the weight given; the mean weights for indication, evaluation, dosage, drug-drug interactions, drug-disease interactions, duplications and therapy duration were respectively; 9.4, 9.6, 6.7, 5.8, 6.6, 7.2 and 6.1. However, this only partly explains the large contribution of these items as their unweighted means (range 0-2 for all seven

items) were 1.07, 0.89, 0.19, 0.01, 0.11, 0.09 and 0.83 respectively (table 6, chapter 3).

The results show that the other four items, i.e. dosage, drug-drug interactions, drug-disease interactions and duplications, score more appropriate. These items can be considered 'pharmaceutical' items. Potentially, this can be attributed to the recent development in the use of electronical prescription systems that control for and thereby prevent drug-drug interactions, drug-disease interactions and duplications in patients' digital medical files. Therefore, these are less dependent on human action and more on electronical systems, which are implemented fairly well in Dutch nursing homes.

Although the absence of multicollinearity and attributions of the independent items to the inappropriateness are promising considering the validity of the index, further analysis must indicate the extent of the constructs' validity by accumulating evidence when hypotheses about the appropriateness of PD prescriptions for NPS in dementia are rejected or confirmed [14] [15]. For example, two more steps, next to multicollinearity analysis, can be taken in the study of nomological validity: 1) the degree to which a construct should behave in relation to other constructs and 2) the construct in isolation measured by reflective measures instead of depicted in the described formative model [15], e.g. by measuring the amount of medication reviews, new indications and evaluations in a year. In addition, in future research other instruments, like the MAI, could very well be used to investigate discriminant validity [15]. However, in that case different outcomes by different instruments should be taken into account; a recent study on discriminant validity on general drug appropriateness measures found that there are differences in reported appropriateness between measures, i.e. Beers criteria 2003, the Screening Tool of Older Person's Potentially Inappropriate Prescriptions (STOPP) and Beers 2012[16][17], which could be due to differences in the definition of the constructs.

Finally, it should be taken into account that the APID index' content, i.e. the formularies for medication prescription[18] and the summary of product characteristics [2], are subject to revisions [19]. If formularies and the SPCs are revised, the APID index should also be updated before a research trial.

Reliability of the APID index

To consistently measure the new construct, it is imperative to have good intra- and interrater reliability, which is a prerequisite for good- research and clinical instruments. Results of the interrater reliability analyses described in chapter 3 show promising agreement on the individual items; the ICCs for agreement of the items are moderate to almost perfect. However, it should

be taken into account that this is not the same as the 'absolute' agreement between raters [20], which varied between the items from 61% to 98%. Therefore, the cause of disagreement between two raters was also studied. The results show that inter-individual differences in information extraction from the patients' files are the major cause of disagreement. If one individual rater extracts information from medical files, the extraction of information from these files is likely to be more identical, which implies that results of intrarater reliability analysis are bound to be higher [21]. However, if the APID index or items from the index are used in clinical practice, a study on the intrarater reliability is recommended.

Medical file research
Given that the APID index uses medical record reports, the extraction of information from the records is an important factor in interrater reliability, as described above. Next to a medical record extraction bias, the results could be biased by the reporting quality.

The independent reliability study reported in chapter 3 found minimal differences between the practising elderly care physician's and the researcher's administration of the APID index, which supports the concept of using medical records for measuring appropriateness; good recordkeeping is a prerequisite for evaluating the PD prescriptions. However, the study also found that physicians, in comparison to the researcher, have additional information about indications. In addition to the information from the medical file, the physician had knowledge at hand.

Another important limitation in relation to medical file research was that for practical reasons a selection method had to be made; the medical charts were used to search for potential continuous inappropriate PD prescriptions with the APID index. That did not account for potential prescription omissions and pro re nata prescriptions, see chapter 4. Therefore, the inappropriateness measurement is limited to continuous prescriptions.

Improvement of appropriate prescription
It was found that biannual medication reviews improve the appropriateness of PD prescriptions. Medication reviews were carried out by pharmacists, physicians and nurses. Pharmacist provided the pharmaceutical information, the side effects associated with PD use, were monitored by physicians. The participation of the nurses in these reviews, which makes it possible to have more detailed information on the patients' present condition in terms of NPS, was considered as one of the strengths. How this interaction added to the improvement should be studied by evaluating the process of implementation. The item 'indication' did not improve significantly by the intervention. This is possible due to that once an indication is made or there is a lack of indication,

the biannual medication review was insufficient in detecting the initial reason for prescription.

Generalisability to other countries

This study was performed in the Netherlands, on so called DSCUs with trained elderly care physicians as the responsible physician. However, the appropriateness of PD prescriptions is a worldwide challenge and similar difficulties with appropriateness, e.g. guideline non- adherence and non-patient factors associated with the prescription of PDs, were found in other countries [22][23][24][25][26][27]. Therefore, the results can very well be generalised to other countries, thus have good external validity.

CLINICAL IMPLICATIONS AND SOCIETAL IMPACT

Worldwide there is an increasing awareness of the importance of the appropriateness of prescriptions [28][29][30][31][32][33][17]. In this thesis appropriateness was defined as the extent of the appropriateness of PD prescriptions on seven individual items. In other studies we found that appropriateness was defined as frequency of use/indications [7] or other particular items, i.e. regularly evaluating the prescriptions [34], the administration and pharmaceutical aspects like dosage, drug-drug interaction, drug-disease interaction and therapy duration[35][36].

This thesis shows that the frequency and the appropriateness of PD prescriptions for NPS in dementia are independent concepts that can be explored separately. This thesis contributed to the knowledge of the appropriateness, when interpreting these new knowledge new implications and recommendations for dementia care arise, which are discussed here:

1) **The majority of psychotropic drug prescriptions for neuropsychiatric symptoms in dementia are inappropriate**

The clinical use of off-label prescriptions of PDs is widespread and persistent[17] [37]; many different PDs are prescribed to patients with similar NPS (chapter 4)[38]. The minority of the PD prescriptions is fully appropriate and non-patient factors are also associated with inappropriate prescriptions. PD prescriptions for NPS in dementia were rated as appropriate when guidelines recommended these specific PDs for a NPS, but even when there is maximum guideline adherence, there still is limited evidence for the efficacy of PD treatment [39] and, therefore, PDs should be regularly evaluated. Additionally, antipsychotics, anxiolytics and hypnotics/sedatives are used too long (chapter 4)[40]. This thesis strengthens the urge for more appropriate PD prescription in dementia.

2) Need for improvement of inappropriate psychotropic drug prescriptions

Estimates are that curing/slowing down the degenerative process in dementia will take another ten years at the least, in the meantime it is advised to address appropriate PD prescriptions [41]. Medication reviews in long-term care settings should be performed annually based on the requirements of the Dutch Healthcare Inspectorate. However, these are time consuming; to increase efficiency a digital support system should be developed/used to assist the medication review processes [42].

To improve health and wellbeing of patients with dementia a balance is needed between effectively treating NPS and taking the negative/side effects of PDs into account [43]. Reviewing medication can improve the appropriateness of drug prescriptions in patients with dementia. This thesis shows that the implementation of structured biannual medication reviews (including education about reviewing and involving the nurse) is an effective method in improving the appropriateness of psychotropic drug prescriptions. Therefore, we recommend the implementation of a structured, repeated medication review with the essential roles of pharmacist, physician and nurse, into daily practice.

3) What to do next and how to do it?

The nursing Home Reform Act (OBRA'87) is a federal American law that sets some standards of care and establishes certain rights for elderly persons in the United States [44]. In the Netherlands, similar laws, the long term care act and the Special Admissions to Psychiatric Hospitals Act (Bopz) [45][46], regulates care for psychiatric patients and thus psychogeriatric nursing home care. Currently, there is a Dutch bill that introduces a roadmap to promote a multidisciplinary approach for voluntary care in regulating NPS in patients with dementia, to prevent involuntary psychogeriatric nursing home care [47].

As mentioned in the introduction of this thesis, the Dutch Healthcare Inspectorate monitors the quality and safety of the care for these patients. The Inspectorate formulated eight points of attention, i.e. quality indicators [48]. These points focus on understanding behaviour and managing behaviour by psychosocial interventions in the first place, and more specifically, attending the topic of this thesis; if PDs are prescribed these should be monitored (by physicians) regularly.

A psychotropic drug monitor could facilitate this using the knowledge from this thesis; a monitor focussing on proper indications, evaluations and therapy durations. The APID index as a research instrument could be adjusted to a self –evaluation tool for physicians. Therefore, the development of such a tool is advised.

If the APID index or items from the APID index are used in clinical practice, intra- and interrater bias should be taken into account. In case of clinical individual use 'absolute' agreement is of importance. If clinicians rate individual PD prescriptions, more information about the method they used to extract the information from the medical file is necessary, when patients transfer to other physicians; to keep clinicians well informed. The results show that the physician could have additional information about their patients' PD indications that could influence the index' score (chapter 3). Additionally, as mentioned in the methodological considerations, the intrarater reliability should be studied.

In relation to the development of a self-evaluation tool an important issue was attended in this thesis; the need for a structured way of extracting information from patient records. The current status of medical file keeping differs between long-term care facilities, i.e. paper files, electronical files or a combination of paper and electronic files. Therefore, a protocol could facilitate the standardized extraction of information that is suited for and can fit different record keeping systems. This protocol should be developed in a way that prevents physicians' bias of self-evaluation; physicians reporting too positive or negative about their own prescriptions. Therefore, electronic systems for pharmaceutical purposes should be implemented to appropriately indicate, evaluate and stop prescriptions in time with, for example, a clinical decision support system [49]. Moreover, this tool should be regularly updated concerning new guideline recommendations and evidence for appropriate PD prescriptions. This updating should be protocolled in time and by a panel consisting of expert pharmacists and physicians that work in the (research) field of PD prescription in dementia.

Another important quality indicator, and point of attention by the Dutch Healthcare Inspectorate, is monitoring the effects of psychosocial and medical interventions biannually [48]. In this thesis we attended to the importance of enforcing these guidelines regularly and based on the results we suggest the development and implementation of a PD self –evaluation tool into clinical practise.

RECOMMENDATIONS FOR FUTURE RESEARCH
Many PDs were prescribed inappropriately, primarily based on off-label and missing indications, missing evaluations and long-term prescriptions. Potentially, physicians overlook to appropriately indicate, evaluate and appropriately stop prescriptions, therefore, determinants of these domains of inappropriate prescriptions should be further explored. Additionally, pro re nata PD prescriptions were not included in this thesis, considering the difficulties in objectifying the rationale of these prescriptions. If PD

prescriptions decrease in the future, potentially pro re nata prescriptions could increase, therefore, future research should include these prescriptions.

Considering the limited knowledge there is about associations of appropriate PD prescriptions for NPS in dementia specifically, qualitative and quantitative research on this topic should be accumulated from other fields of research, e.g. associations with the frequency of PD use [50][51][52][53], to select potential factors associated with appropriateness of PD prescriptions. For example, the factors mentioned in the conceptual framework, chapter 2, could be made up to date with current literature on determinants of (appropriate) PD prescriptions for NPS in dementia and guide the selection of relevant potential determinants of appropriate PD prescriptions in future research. The results from this thesis (chapter 5) show that non-patient factors like nurse's attitudes seem to influence appropriateness of prescriptions, thus, are we treating patients or staff, or both at the same time? Hypothetically, high workloads influence our perception of patients' behaviour and, therefore, result in that caregivers experience patients having NPS and hence in inappropriate PD prescription [54][52][53].

In chapter 7 the implementation of a structured, repeated medication review with the essential roles of pharmacist, physician, and nurse into daily practice is advised to increase the appropriateness, by regularly evaluating the effects and stop PD prescriptions in time. Although suggestions have been made in the methodological considerations of this discussion, future research could give insight into the reason why the appropriateness of indications did not improve by biannual medication reviews. Potentially, by attending to this topic in the education about medication reviews to the multidisciplinary team, this could improve.

Even when there is maximum guideline adherence and thus appropriateness according to the APID index, the evidence for PD prescriptions for NPS is marginal. Therefore, future studies could explore to what extent NPS are reduced by inappropriate prescriptions in comparison to appropriate prescriptions. Moreover, studies have explored the course of NPS during long-term care admission [55][56], however, little is known about the course of NPS in relation to the appropriateness of PD prescription. Longitudinal multicentre studies could potentially lead to insight, for example, into how these symptoms appear during nursing home admission without the use of PDs.

The biopsychological model [8] attributes behaviour, and therefore NPS, to a genetic and an environmental origin. New developments in nursing home care and also new generations of patients with dementia from different backgrounds, could influence the extent with which NPS appear. Therefore, a meta-analysis of research from different decades could lead to insights in

trends, which could lead to new ways to appropriately attend to the needs of long-term care patients and focus on the regulation of NPS.

Furthermore, research should focus on exploring and strengthening the implementation of psychosocial interventions in dementia care and thus regulating NPS, considering these are first choice of treating NPS in dementia and several have been shown to be effective[57]. To effectively regulate NPS, information from patients' representatives is imperative [53], therefore, future implementation studies should address to this topic.

CONCLUDING REMARKS

In conclusion, this thesis adds important knowledge to the field of appropriate dementia care and steps should be taken to implement this knowledge into clinical practice:

- The appropriateness of the prescription of PDs for NPS in nursing home patients with dementia is rather poor, and associated with not only patient – but also non-patient factors.
- Regularly reviewing the medication prescriptions improves the appropriateness of PD prescriptions and the implementation of tools such as the APID index in daily practice, may contribute to increase awareness and hence to a reduction of inappropriate PD use.

The minority of the psychotropic drugs are prescribed appropriately for neuropsychiatric symptoms in dementia; medication reviews contribute to proper treatment.

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APPENDICES

Appendix A

The Appropriate Psychotropic drug use for NPS In Dementia (APID) index, example: **Haloperidol (N05AD01)**

Is there an indication for this drug?	
- In relation to the Psychotropic Drug (PD). - For NPS/sleeping disorder/delirium-> score, for other psychiatric disorders-> do not score. - Find indication from start date to 2 months after / PDs in the history search 6 months after DSCU admission / past 4 months prior to medical record access (for intervention studies).	
	Score
Agitation + Agression, hallucinations / delusions, delirium in dementia.	0
Agitation without aggression, restlessness (no restlessness during the night) in dementia.	1
No or another indication.	2

Is the PD evaluated?	
- In relation to the PD. - Search for evaluation from the start date to 6 months thereafter / PDs prescribed before DSCU admission: search 6 months after DSCU admission / in the past 4 months prior to record access (for intervention studies).	
	Score
- Evaluation found within two weeks from start date / PDs prescribed before DSCU admission: search 6 months after DSCU admission. - For intervention studies, past 4 months prior to record access .	0
Evaluation between 2 weeks and 6 months after start date.	1
Evaluation not found /> 6 months after recording current PG at pf from history.	2

Is the current daily dosage correct?	
Note: If too low, but if there is a documented reduction effort score 0.	Score
With agitation / aggression / hallucinations / delusions 1mg- 6mg (10-60 gtt. of 2mg/ml). Delirium 0.5 mg - 10 mg (5 -100 gtt.).	0
Agitation / agression / hallucinations <1 mg (<10 gtt.) / delirium <0.5 mg (<5 gtt.).	1
Agitation / agression / hallucinations> 6 mg (> 60 gtt.) / delirium> 10 mg (> 100 gtt.).	2

Are there any clinically relevant drug-drug interactions?	
	Score
No.	0
Inductors (bosentan, carbamazepine, fenobarbital, fenytoine, primidon, rifabutine, rifampicine), ritonavir, lopinavir, efavirenz, etravirine, nevirapine.	1
Dopaminergic drugs (amantadine, apomorfine, bromocriptine, levodopa, pergolide, pramipexol, rasagiline, ropinirol, rotigotine, selegiline), antiarrhythmic agents.	2

Are there any clinically relevant drug-disease indications?	
	Score
No.	0
Epilepsy, liver dysfunction, heart failure, prostatic hyperplasia / trophism, sjogren's syndrome, venous thromboembolism.	1
Long-qt syndrome, Parkinson.	2

Is there unnecessary (pseudo) duplication of drugs?	
	Score
No Levomepromazide/ Nozinan, Pipamperon/dipiperon, Zuclopentixol/cisordinol, Olanzepine/zyprexa, Risperdon/risperdal, Clozapine/leponex, Quetiapine/seroquel.	0
Yes, without exceeding the maximum dosage, based on the maximum percentage of the dosage.	1
Yes, exceeding the maximum dosage, based on the maximum percentage of the dosage.	2

Is the duration of the therapy acceptable? Starting from the start date, in case of intermittent use, use the latest start date.	
	Score
< 3 months.	0
> 3 months and <6 months. In case of a documented reduction effort, score 0.	1
> 6 months.	2

Appendix B

The Appropriate Psychotropic drug use for neuropsychiatric symptoms In
Dementia (APID) index, example: **Risperidone (N05AX08)**

Is there an indication for this drug?	
- In relation to the Psychotropic Drug (PD). - For Neuropsychiatric Symptoms (NPS)/sleeping disorder/delirium-> score, for other psychiatric disorders-> do not score. - Find indication from start date to 2 months after / PDs in the history search 6 months after Dementia Special Care Unit (DSCU) admission / past 4 months prior to medical record access (for intervention studies).	
	Score
Agitation, agression, hallucinations / delusions, restlessness during the night in dementia.	0
Delirium in dementia.	1
No or another indication.	2

Is the PD evaluated?	
- In relation to the PD. - Search for evaluation from the start date to 6 months thereafter / PDs prescribed before DSCU admission: search 6 months after DSCU admission / in the past 4 months prior to record access (for intervention studies).	
	Score
- Evaluation found within two weeks from start date / PDs prescribed before DSCU admission: search 6 months after DSCU admission. - For intervention studies, past 4 months prior to record access.	0
Evaluation between 2 weeks and 6 months after start date.	1
Evaluation not found > 6 months after DSCU admission.	2

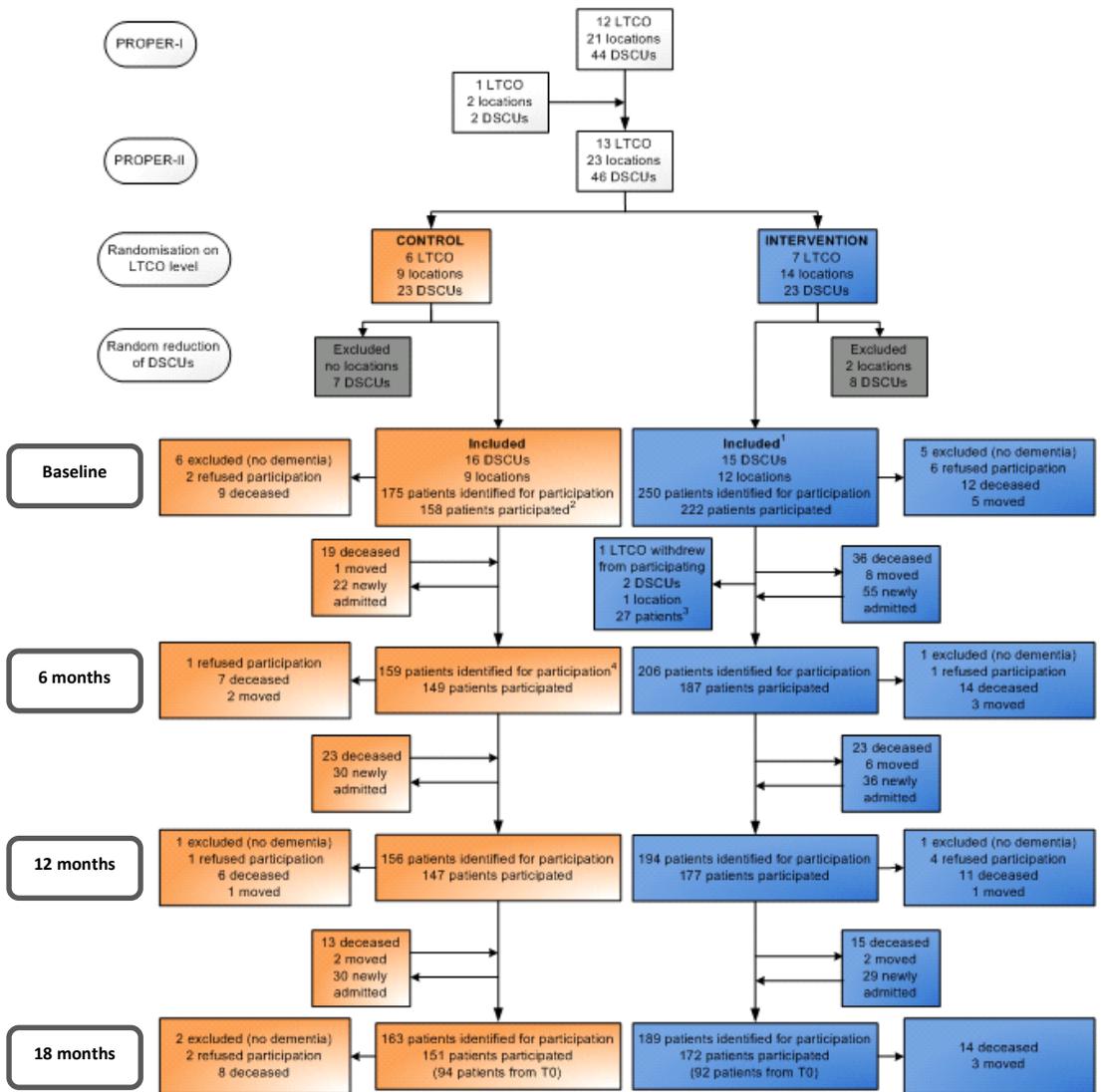| Is the current daily dosage correct?	
Note: If too low, but if there is a documented reduction effort score 0.	Score
With agitation / aggression / hallucinations / delusions / delirium 1mg- 6mg.	0
Agitation / agression / hallucinations / delusions / delirium <1 mg.	1
Agitation / agression / hallucinations / delusions / delirium >6 mg.	2

Are there any clinically relevant drug-drug interactions?	
	Score
No.	0
Inductors (bosentan, carbamazepine, fenobarbital, fenytoine, primidon, rifabutine, rifampicine), ritonavir, lopinavir, indinavir, fluoxetine, paroxetine.	1
Dopaminergic drugs (amantadine, apomorfine, bromocriptine, levodopa, pergolide, pramipexol, rasagiline, ropinirol, rotigotine, selegiline).	2

Are there any clinically relevant drug-disease indications?	
	Score
No.	0
Diabetes Mellitis, epilepsy, hyperlipidemia, heart failure, prostatic hyperplasia / trophism, sjogren's syndrome, venous thromboembolism.	1
Long-qt syndrome, Parkinson.	2

Is there unnecessary (pseudo) duplication of drugs?	
	Score
No Levomepromazide/ Nozinan, Pipamperon/dipiperon, Zuclopentixol/cisordinol, Olanzepine/zyprexa, Haloperidol/Haldol, Clozapine/leponex, Quetiapine/seroquel.	0
Yes, without exceeding the maximum dosage, based on the maximum percentage of the dosage.	1
Yes, exceeding the maximum dosage, based on the maximum percentage of the dosage.	2

Is the duration of the therapy acceptable?	
Starting from the start date, in case of intermittent use, use the latest start date.	Score
< 3 months.	0
> 3 months and <6 months. In case of a documented reduction effort, score 0.	1
> 6 months.	2

Appendix C

Study flowchart for the outcome analysis.
LTCO = Long term care organizations
DSCU = Dementia Special Care Unit
1. Two LTCOs overruled the randomised selection of DSCUs because the selected DSCUs were covered by the same physician and the workload would get too high.
2. A patient was considered a participant if the primary outcome (the appropriateness of psychotropic drug prescription) was collected/assessed.
3. After baseline, one LTCO randomised to the intervention group discontinued the study because of insufficient staffing of physicians.
4. One patient dropped out by mistake and was again included at 18 months.

NEDERLANDSE SAMENVATTING

'Passend psychofarmacagebruik bij dementie'

In 2015 waren er wereldwijd ongeveer 46,8 miljoen mensen met dementie. Intussen neemt de gemiddelde leeftijd van mensen toe en zijn er jaarlijks 9,9 miljoen nieuwe gevallen. Hoewel onderzoek zich richt op preventie, risicofactoren, ziektemanagement, kwaliteit van leven en van zorg, is er nog geen genezing of behandeling die de progressie van de aandoening aanzienlijk vertraagt of stopt.

Dementie is een progressieve hersenaandoening die resulteert in algehele cognitieve achteruitgang en vaak ook gedrag dat als probleem wordt ervaren door de persoon zelf of door mensen in diens omgeving. Voor dit gedrag wordt ook wel de term neuropsychiatrische symptomen (NPS) gebruikt. Voorbeelden van NPS zijn agitatie, agressie, angst, apathie, wanen, depressieve symptomen, hallucinaties en slapeloosheid.

In Nederland verblijft een groot deel van de mensen met vergevorderde dementie op psychogeriatrische afdelingen in verpleeghuizen. Zij zijn meestal ernstig beperkt in verschillende hersenfuncties en vertonen verschillende NPS.

Psychofarmaca worden vaak voorgeschreven voor de behandeling van NPS. Er is echter een toenemende belangstelling voor het verminderen van het gebruik van psychofarmaca bij mensen met dementie die wonen in verpleeghuizen. Richtlijnen wijzen erop dat psychosociale en psychologische interventies, zoals muziektherapie, lichttherapie, snoezelen/ sensorische activatie en psychomotorische therapie, de voorkeursbehandeling van NPS zijn. Psychofarmaca, zoals antipsychotica, antidepressiva, anxiolytica, hypnotica, anti-dementie middelen en anti-epileptica zijn volgens de richtlijnen pas geïndiceerd voor NPS als psychosociale interventies onvoldoende effectief zijn.

Bij de huidige tendens om het aantal voorschriften van psychofarmaca te verminderen, lijkt echter weinig aandacht te bestaan voor de kwaliteit van het voorschrijven zelf. Verbetering van deze kwaliteit kan daarentegen de sleutel zijn voor passend psychofarmacagebruik. Dat wil zeggen, passend volgens de indicaties voor het voorschrijven en het gebruik ervan volgens de richtlijn probleemgedrag van Verenso, de vereniging voor specialisten ouderengeneeskunde. Door passend psychofarmacagebruik te verbeteren kan de effectiviteit toenemen en kunnen de bijwerkingen beperkt blijven. Passend gebruik van psychofarmaca is het onderwerp van dit proefschrift.

Het eerste deel van dit proefschrift richt zich op de ontwikkeling van een index om het construct 'passend psychofarmacagebruik voor NPS bij dementie' te operationaliseren. Tevens komt de huidige status van passend psychofarmacagebruik aan de orde, evenals relevante factoren die mogelijk samenhangen met passend psychofarmacagebruik voor NPS (PROPER I; zie **hoofdstuk 2** voor het studieprotocol).

Het tweede deel van dit proefschrift beschrijft een gerandomiseerde gecontroleerde trial naar de PROPER-interventie. Deze halfjaarlijkse gestructureerde multidisciplinaire medicatiebeoordeling door de arts, apotheker en verpleegkundige/verzorgende werd geïntroduceerd in de interventiegroep; in de controlegroep werd de gebruikelijke zorg voortgezet. Vier maal gedurende 18 maanden werd passend psychofarmacagebruik gemeten met de nieuwe index (PROPER II; zie **hoofdstuk 6** voor het studieprotocol).

PROPER I
Na een algemene inleiding (**hoofdstuk 1**) en een weergave van de onderzoeksopzet van deel 1 (**hoofdstuk 2**), beschrijft **hoofdstuk 3** de ontwikkeling van *the Appropriate Psychotropic drugs use In Dementia index, de APID-index*. Deze is afgeleid van de Medication Appropriateness Index (MAI). De MAI is geschikt voor klinische studies naar medicatiegebruik in het algemeen. De nieuwe index werd specifiek ontwikkeld voor klinische studies naar passend psychofarmacagebruik voor NPS bij bewoners met dementie in verpleeghuizen. De betrouwbaarheid en de validiteit (meet de index ook echt wat bedoeld is) van deze nieuwe index werden onderzocht.

Een panel van deskundigen beoordeelde de MAI items om te bekijken welke items geschikt waren en welke dienden te worden toegevoegd aan de nieuwe index. Een tweede, onafhankelijk expertpanel bepaalde de toepasbaarheid van de nieuwe set van items voor passend psychofarmacagebruik. Vijf bestaande MAI items werden gebruikt, het MAI item 'indicatie' werd aangepast en een nieuw item 'evaluatie' werd toegevoegd. De score-regels werden gebaseerd op richtlijnen, zoals de Verenso richtlijn voor probleemgedrag. Het tweede panel van deskundigen kwam tot de conclusie dat alle items bijdragen aan het concept 'passend psychofarmacagebruik voor NPS bij dementie'. Dit resulteerde in een index met zeven (verschillende) items van passend psychofarmacagebruik. Deze zeven zijn: indicatie, evaluatie (van effectiviteit), dosering, interacties, contra-indicaties, duplicaties en therapieduur. Een studie naar de interbeoordelaarsbetrouwbaarheid (overeenkomst in scores tussen twee invullers) werd uitgevoerd. Zodoende werd de *APID-index* gecreëerd.

Ook werd er een zogenoemde *som score* ontwikkeld, gebaseerd op de gewogen itemscores, om het gebruik van de index in klinische studies

makkelijker toepasbaar te maken. De APID-index som score werd berekend op basis van informatie over individuele psychofarmaca uit de medische dossiers van bewoners. De validiteit werd onderzocht met behulp van een representatieve steekproef van 560 medische dossiers.

Uit de resultaten bleek dat alle items en de som score matige tot bijna perfecte interbeoordelaarsbetrouwbaarheid hadden en dat de validiteit veelbelovend was. De resultaten van deze studie tonen aan dat de APID-index betrouwbaar en valide is voor het meten van passend psychofarmacagebruik voor NPS bij bewoners met dementie in verpleeghuizen in klinische studies.

Hoofdstuk 4 beschrijft de exploratie van de huidige status van passend psychofarmacagebruik voor NPS bij verpleeghuisbewoners met dementie. Een eenmalige meting werd uitgevoerd bij 559 bewoners met dementie die waren opgenomen op psychogeriatrische afdelingen in Nederlandse verpleeghuizen. De mate van passend psychofarmacagebruik werd beoordeeld met behulp van de APID-index.

In totaal werden 578 psychofarmaca gebruikt voor NPS bij 60% van de verpleeghuisbewoners. Slechts tien procent van de psychofarmaca scoorden volledig passend op basis van de APID-index som score. Als het gebruik niet passend was, kwam dit vooral door niet passende indicatie, evaluatie en therapieduur; 36% scoorde volledig passend voor wat betreft de indicatie, 46% scoorde volledig passend voor de evaluatie en 58% scoorde volledig passend voor therapieduur. Antidepressiva werden het meest passend gebruikt en anti-epileptica het minst.

De resultaten impliceren dat psychofarmacagebruik voor NPS bij bewoners met dementie kan worden verbeterd met een focus op passende indicaties, evaluaties en therapieduur.

Hoofdstuk 5 beschrijft het onderzoek naar bewoner- en niet-bewoner gebonden factoren van passend psychofarmacagebruik (zoals ernst van NPS bij bewoners, stress bij de verzorgenden, attitude ten opzichte van dementiezorg van zorgverleners, ervaring van artsen en beschikbare tijd per bewoner). In deze cross-sectionele studie werd de mate van passend gebruik onderzocht met behulp van de APID-index som score. Verschillende metingen werden uitgevoerd om mogelijke bewoner- en niet-bewoner gebonden factoren te identificeren. Data werd verzameld met behulp van vragenlijsten, meetinstrumenten en dossiers van bewoners.

Met behulp van statistische analyses werd bepaald welke van deze factoren verband hielden met de score op de APID-index. De steekproef bestond uit 559 bewoners die in totaal 147 antipsychotica, 167 antidepressiva, 85 anxiolytica en 76 hypnotica gebruikten. Het bleek dat hoe ouder de bewoner en hoe ernstiger de agressie, agitatie, apathie en depressie, hoe

meer passend het psychofarmacagebruik was. Daarentegen was niet-passend psychofarmacagebruik geassocieerd met meer angst bij bewoners, dementie van een ander type dan Alzheimer dementie, meer tijd beschikbaar van de arts per bewoner, meer bewoners per arts, meer jaren ervaring van de arts, en hogere werkdruk van het zorgteam.

Samenvattend bleek dat meer uitgesproken NPS verband hielden met meer passend psychofarmacagebruik. Dit impliceert dat artsen meer aandacht moeten besteden aan psychofarmaca voorschriften als de NPS minder uitgesproken zijn. Er bleken ook enige niet-bewoner gebonden factoren te zijn geassocieerd met de mate van passend psychofarmaca-gebruik. Aangezien sommige van deze bevindingen contra-intuïtief zijn, bijvoorbeeld hoe meer tijd beschikbaar van de arts per bewoner hoe minder passend het psychofarmacagebruik, is meer onderzoek hiernaar nodig.

PROPER-II
Na de weergave van het studieprotocol in hoofdstuk 6, beschrijft **hoofdstuk 7** de effectiviteit van de PROPER-interventie voor het verbeteren van passend psychofarmacagebruik. Tijdens deze studie, met een duur van 18 maanden, werden de medische dossiers van de bewoners om de zes maanden geëvalueerd. De primaire uitkomstmaat was de mate van passend psychofarmacagebruik op basis van de APID-index som score. Bij aanvang van de studie waren er 380 deelnemende bewoners, waarvan er 222 op basis van toeval werden toegewezen aan de interventiegroep (de groep afdelingen die met de medicatiebeoordelingen ging werken). In de controlegroep werd de gebruikelijke zorg voortgezet. De APID-index som score verbeterde in de interventiegroep significant meer dan in de controlegroep wanneer werd gekeken naar alle psychofarmaca voorschriften gezamenlijk. Dit gold ook voor de evaluatie van de effectiviteit en voor de therapieduur van psychofarmaca. Er was geen significant effect van de interventie op de mate van passende indicaties van psychofarmaca voor NPS.

Als dit per psychofarmaca groep werd bepaald, verbeterden de APID-index scores voor de indicatie statistisch significant bij anxiolytica en antidepressiva. Voor hypnotica/sedativa en antidepressiva verbeterde de evaluatie significant. De therapieduur verbeterde significant voor antipsychotica en hypnotica/sedativa.

Op basis van deze resultaten wordt het uitvoeren van een halfjaarlijkse medicatiebeoordeling in het verpleeghuis geadviseerd, waarbij zowel arts, apotheker als een verpleegkundige/verzorgende aanwezig zijn.

Slot opmerkingen

Dit proefschrift voegt belangrijke kennis toe op het gebied van dementiezorg die in de praktijk gebracht kan worden (zie **hoofdstuk 8** voor een beschouwing):

- Psychofarmacagebruik voor NPS bij verpleeghuisbewoners met dementie is vaak niet passend en is geassocieerd met kenmerken van bewoners, maar ook met kenmerken van hun zorgverleners.
- Het regelmatig beoordelen van de psychofarmacavoorschriften verbetert de kwaliteit van het psychofarmacagebruik. Mogelijk kan de implementatie van nieuw te ontwikkelen hulpmiddelen, zoals een voor de dagelijkse praktijk geschikte APID-index, bijdragen aan het vergroten van het bewustzijn van artsen, apothekers en verpleegkundigen/verzorgenden en daarmee aan passend psychofarmacagebruik.

DANKWOORD

Het is ontzettend bijzonder om een aantal jaar aan deze these te hebben gewerkt, met de medewerking van vele anderen. Ruim 700 verpleeghuisbewoners, hun naasten, ruim 100 zorgverleners en mijn collega's. Ik wil met name de bewoners en hun vertegenwoordigers bedanken voor hun medewerking en het beschikbaar stellen van hun anonieme gegevens. Dat geldt ook voor de 13 verpleeghuizen die op verschillende niveaus meewerkten aan de onderzoeken van PROPER I en II. Iedereen heeft zich enorm ingezet en een hoop werk is verzet om de kennis over en de zorg voor patiënten met dementie te verbeteren. Voor hun enthousiasme en inzet wil ik de organisaties, besturen, artsen, apothekers, verpleegkundigen en verzorgers bedanken. Ongelofelijk hoe iedereen, naast zijn of haar drukke baan, tijd heeft weten te vinden om al onze vragenlijsten en formulieren in te vullen. De passie en het enthousiasme die in verpleeghuissetting heerst is indrukwekkend.

Mijn naam staat op de voorkant, maar dit proefschrif is een product van een projectgroep. Graag wil ik daarom nog de leden van projectgroep individueel bedanken.

Debby: zonder je steun, structuur en opbouwende commentaren was het niet gelukt. Bladerend door verschillende dankwoorden van proefschriften van voorgangers, zie ik wat jou zo uniek en goed in je vak maakt. Je hebt altijd een prominente plek in het dankwoord en dat geldt ook voor mijn traject. Ik ken weinig mensen die zo slim, bescheiden, warm en tegelijk doortastend kunnen zijn. Ik ben zeer verheugd dat je universitair hoofddocent bent geworden. Een waardering voor die ongelofelijke inzet die je voor de verpleeghuiszorg levert.

Raymond: ook al ben je een enorme bezige bij, toch sta je altijd klaar voor een inhoudelijk maar bovenal steunend praatje. Je bezit naast een schat aan parate kennis, ook mensenkennis, en bent sympathiek en doortastend op de juiste momenten. Veel dank daarvoor.

Sytse: over jouw raamwerk heb ik mij vrij vaak verwonderd; een encyclopedie. Je bent met zoveel tegelijk bezig, maar toch waren twee woorden genoeg voor jou om te weten waar het over ging. Je kreeg de stoel die daar bij past in Groningen. Ik ben zeer vereerd dat je mijn tweede promotor bent. De humor en relaxedheid die je daarbij uitstraalt, heeft voor mij een meditatief effect.

Naar aanleiding van een sollicitatie voor onderzoeksassistent bij Sandra Zwijsen in Amsterdam, zei Martin 'jij moet zelf promotieonderzoek gaan doen'. Daarna regelde je nog een werkplek voor me bij Gerion, om zo

mijn reistijd van Amsterdam naar Nijmegen wat te verlichten. Je hebt zo veel voor mij en mijn carrière gedaan, dat ik even niet meer weet hoe ik je daar ooit voor kan bedanken. Woorden schieten hier tekort. Je scherpte, behulpzaamheid en de rust die je uitstraalt in je, wat mij lijkt, drukke bestaan, intrigeert me.

Steven: duizendmaal dank voor je enorme hulp met de statistiek. Je wist vaak complexe statistiek tot jip-en-janneketaal te reduceren, zodat ik het ook begreep. Op momenten dat ik even door de bomen het bos niet meer zag, wist je een woud aan variabelen te temmen met een overzichtelijke syntax. Fijn om iemand in de projectgroep te hebben die zo nuchter blijft.

Roland: je hebt me het vak van promovendus geleerd. Toen Claudia en ik van start gingen, was je net klaar en wist je met wijze levenslessen mij klaar te stomen voor een lange intensieve tijd als promovendus. Incasseren, tandenknarsen en omzetten in positieve energie om tot mooi gedegen onderzoek te komen. Ik ben je daar erg dankbaar voor.

Marjorie: je was mijn heldin op het gebied van farmaca. Erg fijn om iemand bij het project te hebben met zoveel parate farmaceutische kennis. Naast de inhoud, hebben we de strategie om de APID index up to date te houden aan jou te danken.

Claudia: het was enorm leuk en vooral ook erg leerzaam met je samen te werken. Je had al veel ervaring in het uitvoeren van onderzoek, waardoor ik in het begin van het project met je mee kon surfen. Hier heb ik veel van je geleerd en daar wil ik je graag voor bedanken. Bedankt ook voor de lol die we samen hadden en de gezelligheid die dat in het, soms lastige, werk meebracht.

Erica: met dank aan je structuur en steun, kan ik nu nog steeds terugvinden hoe we dingen een aantal jaar geleden hebben gedaan. Hoe verder ik in het traject verzeild raakte, hoe dankbaarder ik je ben. Je was en bent een steun en toeverlaat en ik ben verheugd om te horen dat het onderzoek je niet loslaat. Ik ben vereerd dat je paranimf wilt zijn.

Natuurlijk wil ik ook mijn familie, (zeil)vrienden, andere collega's en speciaal Marloes bedanken voor hun steun tijdens en interesse in mijn promotietraject. Af en toe vertellen wat je nu eigenlijk de hele tijd aan het doen bent, helpt het denkproces enorm. Zo wordt het ook mogelijk om soms ogenschijnlijk complexe materie weer nuchter en simpel te bekijken.

Mam: je was al veelvuldig paranimf in je loopbaan en je kent het verpleeghuis als revalidant. Een enorme eer dat je ook mijn paranimf wilt zijn.

Olivia: sinds je in mijn leven bent, zorg je voor dierbare momenten. Voor jou geldt eerst zien dan geloven, houd het vast.

CURRICULUM VITAE

Klaas van der Spek is zoon van een psychoanalyticus (vader) en biomedisch wetenschapper (moeder), waardoor zijn interesse voor psychologie en de wetenschap met de paplepel is ingegoten. Hij is in 1983 geboren in Alkmaar. Na het afronden van zijn VWO in 2002, startte hij aan de TU Delft met de opleiding Maritieme Techniek. In 2004 maakte hij de switch naar psychologie en ging studeren aan de VU. Naast zijn opleiding werkte hij op een kleine scheepswerf op het NDSM terrein in Amsterdam. De interesse voor de neuropsychologie; het brein als complexe rekenmachine en de fysiologie erachter, was er altijd al. Hierbij trok hem met name de ontdekkingstocht naar het onbekende zijn interesse. Tijdens de master klinische neuropsychologie kreeg de verpleeghuiszorg zijn aandacht. Hij liep zijn praktijkstage in Revalidatiecentrum Amsterdam en werkte, tijdens en na het afronden van zijn studie, als onderzoeksassistent op de afdeling klinische neuropsychologie mee aan een promotieonderzoek van Bart Plooij over pijn bij dementie. Hij startte in 2011 met zijn eigen promotieonderzoek op de afdeling Eerstelijnsgeneeskunde aan het Radboudumc. Daarnaast werkte hij in de gespecialiseerde GGZ en forensische psychiatrie. Tijdens een uitzendklus medio 2014, werd zijn interesse gewekt door de complexiteit en de tweestrijd tussen behandelen en beveiligen in de forensische zorg. Eind 2014 kreeg hij een baan aangeboden bij de Oostvaarderskliniek waar hij begin 2016 de mogelijkheid kreeg om te starten met de opleiding tot GZ-psycholoog. In zijn vrije tijd is Klaas een fanatiek wedstrijdzeiler in de Laser Standaard, Flying Dutchman en Valkenklasse. Daarnaast loopt hij hard en zit hij graag op zijn wielrenfiets.

Er is een toenemende belangstelling voor het verminderen van psychofarmacagebruik voor de behandeling van neuropsychiatrische symptomen (NPS) bij patiënten met dementie in verpleeghuizen. Richtlijnen adviseren psychosociale interventies bij de behandeling van NPS, en psychofarmaca als deze psychosociale interventies onvoldoende effectief zijn. De initiatieven om het gebruik van psychofarmaca te verminderen lijken echter weinig aandacht te hebben voor de kwaliteit van het voorschrijven zelf. Dit kan daarentegen de sleutel zijn voor passend gebruik, met mogelijk meer effectiviteit en minder bijwerkingen tot gevolg. Passend gebruik van psychofarmaca bij dementie is het onderwerp van dit proefschrift.