Psychopharmacological treatment of neuropsychiatric symptoms

proper prescription in perspective

Claudia Smeets

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Colofon

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Psychopharmacological treatment of neuropsychiatric symptoms

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Claudia Hendrina Wilhelmina Smeets

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Promotoren

Prof. dr. R.T.C.M. Koopmans

Prof. dr. S.U. Zuidema (Universitair Medisch Centrum Groningen)

Prof. dr. D.L. Gerritsen

Copromotor

Dr. M. Smalbrugge (Amsterdam Universitair Medische Centra)

Manuscriptcommissie

Prof. dr. C. Kramers

Prof. dr. C.R.L. Boot

Prof. dr. W.P. Achterberg (Leids Universitair Medisch Centrum)

Contents

Verzorgende: En sommige mensen worden dan zo opgejaagd [...] Die ene bewoner bij ons [...], die jaagt zijn eigen helemaal op: zijn hart gaat helemaal te keer, krijgt helemaal een rood hoofd, je kunt hem niet meer doorgronden. Maar geven we hem een pilletje [...] dan is hij de hele dag helemaal onder zeil. Dus ja, waar kies je dan voor?

(16867:17167) - D10: V0904

Chapter 1

General introduction

Introduction

Whereas cognitive problems are the main hallmark of dementia, almost all nursing home patients with dementia additionally develop neuropsychiatric symptoms [1, 2]. These encompass a wide spectrum of symptoms such as agitation, psychosis, depression, anxiety, and apathy. Neuropsychiatric symptoms are also defined as 'behavior in which suffering or danger is involved for the person with dementia or others' [3]. Neuropsychiatric symptoms can be challenging for patients themselves and for those who surround them, such as caregivers, spouse, and other residents. It is known that neuropsychiatric symptoms can negatively affect the patients' quality of life and are a frequent reason for nursing home admission [4-8].

In the Netherlands, long-term care for patients with dementia differs from other countries. In Dutch nursing homes, it is common that patients with advanced dementia reside in Dementia Special Care Units. They are treated by a multidisciplinary team employed by the nursing home. This team generally includes a physician who is educated as elderly care physician, several nurses and nurse assistants, one of whom is primarily responsible ('Eerst Verantwoordelijk Verzorgende'), a psychologist, and paramedics [9-11].

It is common that neuropsychiatric symptoms among nursing home patients with dementia are treated with psychotropic drugs such as antipsychotics, antidepressants, anxiolytics, and hypnotics [12]. This is remarkable, not only since the evidence for effectiveness of psychotropic drugs on neuropsychiatric symptoms is limited, but also because they can cause severe side effects [13, 14]. Especially antipsychotics are notorious for their sedative effects and for causing extrapyramidal symptoms, cerebrovascular events, and urinary tract infections. The use of antipsychotics is furthermore related to enlarged risks of falls, pneumonia, and potentially mortality [15-21]. Also antidepressants can cause side effects such as gastrointestinal complaints, headache, sleep disturbances, cardiac side effects, and sedation [22], and anxiolytics and hypnotics give increased risks on falls and physical disability [23, 24].

Ever since the use of antipsychotics started for the treatment of neuropsychiatric symptoms in the mid fifties, side effects have been described [25, 26]. Initially, the sedative effects of the antipsychotic drug chlorpromazine were introduced as a possible solution for the 'shortage of nursing staff, owing to which large wards of noisy, difficult patients have to be in the care of too few nurses, or patients have to be left at night with inadequate supervision' [26]. Later on, the prescription of antipsychotics and other psychotropic drugs became more controversial and was connected with terms such as 'chemical restraints', 'inappropriate', and 'misuse' [27, 28]. Recommendations for starting with a small dose, and gradually increasing this to find the lowest effective dose, regular efforts for dose reduction or discontinuation, and monitoring were stipulated [28]. Since the eighties, this critical attitude toward the prescription of especially antipsychotics remained, mainly with a pharmacological focus [29-31].

Neuropsychiatric symptoms are not necessarily treated with psychotropic drugs, there are also psychosocial interventions. Especially therapeutical activities that are adapted to the patient's preferences appear effective to reduce agitation, depressive symptoms, and apathy [3]. Such activities can include listening to, or making music, participating in creative or physical activities, playing games, but also getting a massage. Education for nurses or next of kin on how to deal with personal preferences could be effective as well. For depressive symptoms specifically, cognitive behavioral therapy may help . Although the certainty of evidence of these psychosocial interventions from randomized controlled trials is low, there are no signs that these therapies cause harm either [3].

Authorities exert pressure not to opt for drugs when treating neuropsychiatric symptoms. In 2005 and 2008, the United States Food and Drug Administration warned for increased risk of death in patients with dementia treated with antipsychotics [32]. Also, the Dutch 'College ter Beoordeling van Geneesmiddelen (CBG)', who balances benefits with side effects prior to registration of drugs for a specific indication on the Dutch market, has not approved psychotropic drugs for neuropsychiatric symptoms. The CBG made an exception for risperidone only to treat severe restlessness and psychotic symptoms [33]. Further, guidelines strongly advise against the prescription of psychotropic drugs [3, 34]. They usually recommend starting with a profound multidisciplinary analysis of the neuropsychiatric symptoms that require intervention. Underlying causes should be addressed, e.g. by treatment of somatic causes or avoiding factors that provoke the symptoms. Only if this approach is insufficient, the prescription of psycho-tropic drugs may be considered. In these cases, prescribing should be done according to a clear treatment plan, with frequent evaluation, and a strategy for discontinuation [3].

Prevention and psychosocial treatment of neuropsychiatric symptoms have probably improved within the last decades. Nursing home residents with dementia currently have more privacy, use less physical restraints, and are involved in a larger variety of activities [35, 36]. Care personnel has a more patient-centered attitude, and there are more nurses with higher educational levels. It has become increasingly important that patients – as far as possible – retain control of their lives and have the freedom to make their own choices within a long-term care institution [37]. In addition, several multidisciplinary interventions have been developed that aim to improve the treatment of neuropsychiatric symptoms [38-40].

Despite the pressure against prescription and the improvements in prevention and psychosocial treatment of neuropsychiatric symptoms, it is striking that psychotropic drugs are still widely used. In order to improve prescription it is important to understand why psychotropic drugs are prescribed and to search for an intervention that improves the prescription among nursing home patients with dementia.

Objective and outline of this thesis

The objective of this thesis is to find new angles on improving the psychopharmacological treatment of neuropsychiatric symptoms of nursing home patients with dementia. This thesis addresses following research questions:

1. *Which factors are involved in the prescription of psychotropic drugs for neuropsychiatric symptoms in patients with dementia?*

Chapter 2 describes the design of a mixed methods approach to unravel which factors are associated with the prescription of psychotropic drugs. Chapter 3 presents the qualitative, and chapter 4 the exploratory quantitative results. Chapter 4 also shows prevalence rates of psychotropic drugs. Chapter 5 reports about the impact of methodological decisions in trials on the pooled effect sizes of antipsychotics, which sheds a light on the progressing insights that contribute to proper prescription.

2. *Is structured and repeated multidisciplinary medication review effective in reducing psychotropic drug prescription?*

Chapter 6 describes the design of a trial to study the effect of the PROPER intervention. The results are presented in chapter 7.

References

1. Selbaek, G., et al., *The course of neuropsychiatric symptoms in nursing-home patients with dementia over a 53-month follow-up period.* Int Psychogeriatr, 2014. **26**(1): p. 81-91.
2. Zhao, Q.F., et al., *The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis.* J Affect Disord, 2016. **190**: p. 264-71.
3. Zuidema SU, S.M., Bil WME, Geelen R, Kok RM, Luijendijk HJ, van der Stelt I, van Strien AM, Vink MT, Vreeken HL., *Multidisciplinary Guideline problem behaviour in dementia*. 2018: Utrecht
4. Mjorud, M., et al., *Variables associated to quality of life among nursing home patients with dementia.* Aging Ment Health, 2014: p. 1-9.
5. van de Ven-Vakhteeva, J., et al., *The impact of antipsychotics and neuropsychiatric symptoms on the quality of life of people with dementia living in nursing homes.* Int J Geriatr Psychiatry, 2012.
6. Feast, A., et al., *A systematic review of the relationship between behavioral and psychological symptoms (BPSD) and caregiver well-being.* Int Psychogeriatr, 2016. **28**(11): p. 1761-1774.
7. Gerritsen, D.L., et al., *The Difficulty With Studying Challenging Behavior.* J Am Med Dir Assoc, 2019.
8. Gaugler, J.E., et al., *Predictors of nursing home admission for persons with dementia.* Med Care, 2009. **47**(2): p. 191-8.
9. Koopmans, R.T.C.M., M. Pellegrom, and E.R. van der Geer, *The Dutch Move Beyond the Concept of Nursing Home Physician Specialists.* J Am Med Dir Assoc, 2017. **18**(9): p. 746-749.
10. Verenso. *Scholing en bijeenkomsten - Kaderopleidingen* 6 March 2019]; Available from: www.verenso.nl/scholing-en-bijeenkomsten/kaderopleidingen.
11. Sectie Ouderenpsychologie Nederlands Instituut van Psychologen, *De psycholoog in de veranderende verpleeghuiszorg*. 2016.
12. Janus, S.I., et al., *Psychotropic drug prescriptions in Western European nursing homes.* Int Psychogeriatr, 2016. **28**(11): p. 1775-1790.
13. Wang, J., et al., *Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis.* J Neurol Neurosurg Psychiatry, 2015. **86**(1): p. 101-9.
14. Seitz, D.P., et al., *Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic review.* Int Psychogeriatr, 2013. **25**(2): p. 185-203.
15. Tariot, P.N., L.A. Profenno, and M.S. Ismail, *Efficacy of atypical antipsychotics in elderly patients with dementia.* J Clin Psychiatry, 2004. **65 Suppl 11**: p. 11-5.
16. Knol, W., et al., *Antipsychotic drug use and risk of pneumonia in elderly people.* J Am Geriatr Soc, 2008. **56**(4): p. 661-6.
17. van Strien, A.M., et al., *Association Between Urinary Tract Infections and Antipsychotic Drug Use in Older Adults.* J Clin Psychopharmacol, 2018. **38**(4): p. 296-301.
18. Sacchetti, E., C. Turrina, and P. Valsecchi, *Cerebrovascular accidents in elderly people treated with antipsychotic drugs: a systematic review.* Drug Saf, 2010. **33**(4): p. 273-88.
19. Ballard, C. and J. Waite, *The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease.* Cochrane Database Syst Rev, 2006(1): p. CD003476.
20. Gill, S.S. and D.P. Seitz, *Association of antipsychotics with mortality among elderly patients with dementia.* Am J Geriatr Psychiatry, 2007. **15**(11): p. 983-4; author reply 984-5.

21. Hulshof, T.A., et al., *The Mortality Risk of Conventional Antipsychotics in Elderly Patients: A Systematic Review and Meta-analysis of Randomized Placebo-Controlled Trials.* J Am Med Dir Assoc, 2015. **16**(10): p. 817-24.
22. Kok, R.M. and C.F. Reynolds, 3rd, *Management of Depression in Older Adults: A Review.* Jama, 2017. **317**(20): p. 2114-2122.
23. Gray, S.L., et al., *Benzodiazepine use and physical disability in community-dwelling older adults.* J Am Geriatr Soc, 2006. **54**(2): p. 224-30.
24. Fonad, E., et al., *Falls and fall risk among nursing home residents.* J Clin Nurs, 2008. **17**(1): p. 126-34.
25. Winkelman, N.W., Jr., *Chlorpromazine in the treatment of neuropsychiatric disorders.* J Am Med Assoc, 1954. **155**(1): p. 18-21.
26. Seager, C.P., *Chlorpromazine in treatment of elderly psychotic women.* Br Med J, 1955. **1**(4918): p. 882-5.
27. Covert, A.B., T. Rodrigues, and K. Solomon, *The use of mechanical and chemical restraints in nursing homes.* J Am Geriatr Soc, 1977. **25**(2): p. 85-9.
28. van Praag, H.M., *Psychotropic drugs in the aged.* Compr Psychiatry, 1977. **18**(5): p. 429-42.
29. Willekens-Bogaers, M.A. and E.J. Vollaard, *[Neuroleptics in psychogeriatrics. A proposal for a more rational prescription policy].* Tijdschr Gerontol Geriatr, 1985. **16**(5): p. 179-89.
30. Koopmans, R.T., et al., *[Use of psychotropic drugs in a group of nursing home patients with dementia: many users, long-term use but low dosages].* Tijdschr Gerontol Geriatr, 1993. **24**(6): p. 214-9.
31. Willekens-Bogaers, M.A. and G.W. Smits, *[Neuroleptics in psychogeriatrics. Evaluation of a treatment proposal].* Tijdschr Gerontol Geriatr, 1990. **21**(3): p. 99-107.
32. FDA U.S. Food and Drug Administration. *Postmarket Drug Safety Information for Patients and Providers FDA ALERT [6/16/2008].* 27 March 2019]; Available from: https://wayback.archive-it.org/7993/20170722190727/https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm.
33. Oudewortel, L., *Antipsychotica bij probleemgedrag bij dementie in verpleeg- en verzorgingshuizen.* Geneesmiddelenbulletin, 2013. **47**(3): p. 27-33.
34. Nederlandse Vereniging voor Klinische Geriatrie, *Richtlijn Diagnostiek en Behandeling van dementie.* 2014.
35. Prins, M., C. Heijkants, and B. Willemse, *Onbegrepen gedrag in de verpleeghuiszorg voor mensen met dementie. Monitor Woonvormen Dementie*. 2018, Trimbos-instituut: Utrecht.
36. Ministerie van Volksgezondheid Welzijn en Sport, *De maatschappij verandert. Verandert de zorg mee?* 2014.
37. Zorginstituut Nederland, *Kwaliteitskader Verpleeghuiszorg.* 2017.
38. Leontjevas, R., et al., *A structural multidisciplinary approach to depression management in nursing-home residents: a multicentre, stepped-wedge cluster-randomised trial.* Lancet, 2013. **381**(9885): p. 2255-64.
39. Zwijsen, S.A., et al., *Coming to grips with challenging behavior: a cluster randomized controlled trial on the effects of a multidisciplinary care program for challenging behavior in dementia.* J Am Med Dir Assoc, 2014. **15**(7): p. 531 e1-531 e10.
40. Pieper, M.J., et al., *Effects of a Stepwise Multidisciplinary Intervention for Challenging Behavior in Advanced Dementia: A Cluster Randomized Controlled Trial.* J Am Geriatr Soc, 2016. **64**(2): p. 261-9.

Verzorgende: Het is niet dat ik er last van heb, dat ze de hele tijd achter me aan loopt, maar ze weet zelf met haar eigen ook geen raad. Die zie je ook doodongelukkig over de afdeling lopen. En dan heb ik zoiets van: nou als je dan onrustmedicatie geeft, dan kan ik me daar wel in vinden.

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Chapter 2

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

BMC Psychiatry, 2013. 13(1): p. 307

Klaas van der Spek

Debby L. Gerritsen

Martin Smalbrugge

Marjorie H.J.M.G. Nelissen-Vrancken

Roland B. Wetzels

Claudia H.W. Smeets

Sytse U. Zuidema

Raymond T.C.M. Koopmans

Abstract

Background: Nursing home patients with dementia use psychotropic drugs longer and more frequently than recommended by guidelines implying that 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 6 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. Factors 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.

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) [4-6]. 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% [6, 8, 9]. It is also known that antipsychotic use varies among countries between 11% and 52% [6, 10-12].

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 [13-15]. 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].

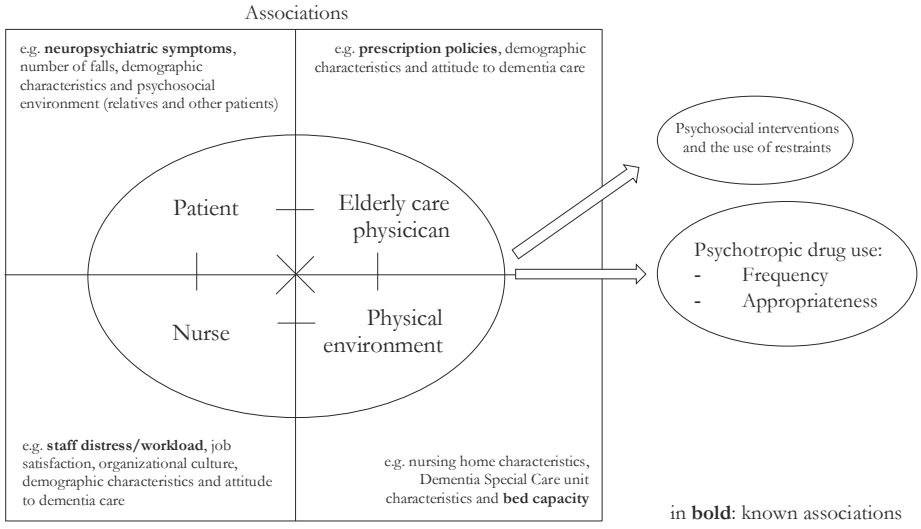
PDU varies considerably among nursing homes and DSCUs [24, 25]. This could partly be explained by different prevalence rates of NPS among patients on DSCUs [3]. However there is growing evidence that this inter-DSCU variation in PDU is not only related to the severity of patients' NPS [6, 26]. The PDU 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 4 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 4 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

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 [28], 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 6 nursing homes with high and 6 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 2 out of 3 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 [29] 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 [30] to determine the drug's appropriateness for individual patients on 10 items and is proven to be reliable [31] and applicable in the Dutch nursing home setting [32]. 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) [33]. PD information that is not provided by the Dutch Verenso guideline, will be derived from 'Farmacotherapeutisch Kompas' [34], published by the Dutch Health Care Insurance Board (CVZ) and based on the summary of product characteristics (SPC) [35]. 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) [36, 37]. The NPI-Q assesses NPS in dementia and caregiver distress. The NPI-Q measures the occurrence and severity of NPS on a 3-point Likert scale and associated caregiver burden on a 5-point Likert scale. Additionally, frequency of agitation and aggression will be assessed with the Cohen-Mansfield Aggression Inventory

(CMAI) [38], of which the original and the translated Dutch version has been proven reliable and valid [39, 40]. The CMAI consists of 29 individual items, each rated at a 7-point Likert scale, combined to 3 subscales of (physically) aggressive, physically non-aggressive and verbally agitated behavior [39]. 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) [41] . The ADQ consists of 19 items, on a 5-point Likert scale and measures hopefulness and person-centeredness 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) [42], the validated Dutch version [43], a 6-item scale where 4 phrases need to be set in an order of personal relevance. The CVFS assesses the 6 dimensions of the competing values framework [44]: 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 [45, 46]. This scale consists of 10 items about unit workload, each item can be scored on a 5-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 4-point Likert scale for each item, also a score on another 4-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) [47, 48]; a 21-item, 5-point Likert scale that focuses on nursing staff satisfaction. It consists of 7 subscales with 3 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) [41]. 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 (see Table 1).

Table 1: Mixed methods research parameters/instruments

	Parameters	Instruments	Registered by
Quantitative			
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			
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. Sixty-seven percent 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 12 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 refs [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 subject 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 toward safer PDU.

References

1. Health Council of the Netherlands, *Dementia*. 2002: The Hague.
2. Volksgezondheid Toekomst Verkenning. *Hoe vaak komt dementie voor en hoeveel mensen sterven eraan?*; Available from: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/psychische-stoornissen/dementie/omvang.
3. Zuidema, S.U., et al., *Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia.* Int J Geriatr Psychiatry, 2007. **22**(7): p. 632-8.
4. Cornege-Blokland, E., et al., *Reasons to prescribe antipsychotics for the behavioral symptoms of dementia: a survey in Dutch nursing homes among physicians, nurses, and family caregivers.* J Am Med Dir Assoc, 2012. **13**(1): p. 80 e1-6.
5. Wood-Mitchell, A., et al., *Factors influencing the prescribing of medications by old age psychiatrists for behavioural and psychological symptoms of dementia: a qualitative study.* Age Ageing, 2008. **37**(5): p. 547-52.
6. Nijk, R.M., S.U. Zuidema, and R.T. Koopmans, *Prevalence and correlates of psychotropic drug use in Dutch nursing-home patients with dementia.* Int Psychogeriatr, 2009. **21**(3): p. 485-93.
7. Enmarker, I., R. Olsen, and O. Hellzen, *Management of person with dementia with aggressive and violent behaviour: a systematic literature review.* Int J Older People Nurs, 2011. **6**(2): p. 153-62.
8. Selbaek, G., O. Kirkevold, and K. Engedal, *The prevalence of psychiatric symptoms and behavioural disturbances and the use of psychotropic drugs in Norwegian nursing homes.* Int J Geriatr Psychiatry, 2007. **22**(9): p. 843-9.
9. Wetzels, R.B., et al., *Prescribing pattern of psychotropic drugs in nursing home residents with dementia.* Int Psychogeriatr, 2011. **23**(8): p. 1249-59.
10. Feng, Z., et al., *Use of physical restraints and antipsychotic medications in nursing homes: a cross-national study.* Int J Geriatr Psychiatry, 2009. **24**(10): p. 1110-8.
11. Testad, I., et al., *Nursing home structure and association with agitation and use of psychotropic drugs in nursing home residents in three countries: Norway, Austria and England.* Int J Geriatr Psychiatry, 2010. **25**(7): p. 725-31.
12. Nygaard HA, B.E., Juvik OB, Pedersen WE, Rotevatn TS, Vollset A, *Consumption of psychotropic drugs in nursing home residents: A prospective study in patients permanently admitted to a nursing home.* International Journal of Geriatric Psychiatry, 1994. **9**(5): p. 387-391.
13. van Iersel, M.B., et al., *Antipsychotics for behavioural and psychological problems in elderly people with dementia: a systematic review of adverse events.* Drugs Aging, 2005. **22**(10): p. 845-58.
14. Schneider, L.S., K. Dagerman, and P.S. Insel, *Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials.* Am J Geriatr Psychiatry, 2006. **14**(3): p. 191-210.
15. Ballard, C., et al., *The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial.* Lancet Neurol, 2009. **8**(2): p. 151-7.

16. Uzun, S., et al., *Side effects of treatment with benzodiazepines.* Psychiatr Danub, 2010. **22**(1): p. 90-3.
17. Wetzels, R.B., et al., *Determinants of quality of life in nursing home residents with dementia.* Dement Geriatr Cogn Disord, 2010. **29**(3): p. 189-97.
18. Ballard, C., et al., *Quality of life for people with dementia living in residential and nursing home care: the impact of performance on activities of daily living, behavioral and psychological symptoms, language skills, and psychotropic drugs.* Int Psychogeriatr, 2001. **13**(1): p. 93-106.
19. Gustafsson, M., S. Karlsson, and H. Lovheim, *Inappropriate long-term use of antipsychotic drugs is common among people with dementia living in specialized care units.* BMC Pharmacol Toxicol, 2013. **14**: p. 10.
20. van Dijk, K.N., et al., *Drug utilisation in Dutch nursing homes.* Eur J Clin Pharmacol, 2000. **55**(10): p. 765-71.
21. Zuidema, S.U., et al., *Neuropsychiatric symptoms in nursing home patients: factor structure invariance of the Dutch nursing home version of the neuropsychiatric inventory in different stages of dementia.* Dement Geriatr Cogn Disord, 2007. **24**(3): p. 169-76.
22. Bustin, J., *[Atypical antipsychotics and CATIE-AD. Is this a turning point?].* Vertex, 2009. **20**(84): p. 136-43.
23. Smalbrugge, M., et al., *Guideline problem behavior*, in 2008: Utrecht.
24. Chen, Y., et al., *Unexplained variation across US nursing homes in antipsychotic prescribing rates.* Arch Intern Med, 2010. **170**(1): p. 89-95.
25. Zuidema, S.U., et al., *Psychotropic drug prescription in nursing home patients with dementia: influence of environmental correlates and staff distress on physicians' prescription behavior.* Int Psychogeriatr, 2011. **23**(10): p. 1632-9.
26. Zuidema, S.U., et al., *Environmental correlates of neuropsychiatric symptoms in nursing home patients with dementia.* Int J Geriatr Psychiatry, 2010. **25**(1): p. 14-22.
27. Kamble, P., et al., *Use of antipsychotics among elderly nursing home residents with dementia in the US: an analysis of National Survey Data.* Drugs Aging, 2009. **26**(6): p. 483-92.
28. Smeets, C.H., et al., *Improving psychotropic drug prescription in nursing home patients with dementia: design of a cluster randomized controlled trial.* BMC Psychiatry, 2013. **13**(1): p. 280.
29. Nordic Council on Medicines, *Guidelines for ATC classification*. 1990, WHO Collaborating Center for Drugs Statistics Methodology: Oslo.
30. Hanlon, J.T., et al., *A method for assessing drug therapy appropriateness.* J Clin Epidemiol, 1992. **45**(10): p. 1045-51.
31. Luo, R., et al., *Comparison of tools for the assessment of inappropriate prescribing in hospitalized older people.* J Eval Clin Pract, 2012. **18**(6): p. 1196-202.
32. Stuijt, C.C., et al., *Appropriateness of prescribing among elderly patients in a Dutch residential home: observational study of outcomes after a pharmacist-led medication review.* Drugs Aging, 2008. **25**(11): p. 947-54.
33. *KNMP Kennisbank*. Available from: http://www.kennisbank.knmp.nl/index.asp.
34. *Farmacotherapeutisch Kompas*. Available from: http://www.fk.cvz.nl/.

35. Medicines Evaluation Board. Available from: http://www.cbg-meb.nl/cbg/en/default.htm.
36. Kaufer, D.I., et al., *Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory*. J Neuropsychiatry Clin Neurosci, 2000. **12**(2): p. 233-9.
37. de Jonghe, J.F., et al., *[Neuropsychiatric inventory questionnaire (NPI-Q): A validity study of the Dutch form]*. Tijdschr Gerontol Geriatr, 2003. **34**(2): p. 74-7.
38. Cohen-Mansfield, J. and N. Billig, *Agitated behaviors in the elderly. I. A conceptual review*. J Am Geriatr Soc, 1986. **34**(10): p. 711-21.
39. Zuidema, S.U., et al., *Assessing neuropsychiatric symptoms in nursing home patients with dementia: reliability and Reliable Change Index of the Neuropsychiatric Inventory and the Cohen-Mansfield Agitation Inventory*. Int J Geriatr Psychiatry, 2011. **26**(2): p. 127-34.
40. Zuidema, S., R. Koopmans, and F. Verhey, *Prevalence and predictors of neuropsychiatric symptoms in cognitively impaired nursing home patients*. J Geriatr Psychiatry Neurol, 2007. **20**(1): p. 41-9.
41. Lintern, T., *Quality in Dementia Care: Evaluating Staff Attitudes and Behaviour. PhD Thesis*. 2001, University of Wales: Bangor.
42. Scott-Cawiezell, J., et al., *Nursing home culture: a critical component in sustained improvement*. J Nurs Care Qual, 2005. **20**(4): p. 341-8.
43. van Beek, A.P. and D.L. Gerritsen, *The relationship between organizational culture of nursing staff and quality of care for residents with dementia: questionnaire surveys and systematic observations in nursing homes*. Int J Nurs Stud, 2010. **47**(10): p. 1274-82.
44. Cameron, K.F.S., *Culture, congruence, strenght and type: relationship to effectiveness*. Res Org Change Dev, 1991(5): p. 23–58.
45. de Jonge, J. and J.A. Landeweerd, *Toetsing van de job demand-control benadering bij werknemers in de gezondheidszorg: een secundaire data-analyse [Testing of the Job approach among health care workers: a secondary analysis]*. Gedrag en Organisatie, 1993(6): p. 79–92.
46. Vermaat, K., *Flexibele werklastbeheersing in de verpleging [Flexible workload control in nursing]*, in *Universty of Limburg*. 1994: Maastricht.
47. Landeweerd JA, B.N., Nissen JMF., *Arbeidsvoldoening bij verplegenden en verzorgenden. De Maastrichtse arbeidssatisfactieschaal voor de gezondheidszorg [Job satisfaction of nurses and nursing assistants. The Maastricht Work Satisfaction Scale for Healthcare.]*, in *Handboek Verpleegkundige innovatie*. 1996, Bohn Stafleu: Houten.
48. Sloane, P.D., et al., *The Therapeutic Environment Screening Survey for Nursing Homes (TESS-NH): an observational instrument for assessing the physical environment of institutional settings for persons with dementia*. J Gerontol B Psychol Sci Soc Sci, 2002. **57**(2): p. S69-78.
49. Cooney, A., *Choosing between Glaser and Strauss: an example*. Nurse Res, 2010. **17**(4): p. 18-28.
50. Strauss, A. and J. Corbin, *Basics of Qualitative Research*. 3rd ed. 2008, Thousand Oaks, CA: Sage.

51. Strauss, A., *Basics of qualitative research; Grounded theory procedures and techniques.* 1990, London: Sage.
52. Peduzzi, P., et al., *A simulation study of the number of events per variable in logistic regression analysis.* J Clin Epidemiol, 1996. **49**(12): p. 1373-9.
53. Peduzzi, P., et al., *Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates.* J Clin Epidemiol, 1995. **48**(12): p. 1503-10.

Verzorgende: Er wordt zo vaak nog gewoon naar ons gekeken van: redden wij het niet? [...] Wij zijn hier voor de mensen, ik kom hier voor de mensen [...]. De mensen hoeven niet voor een leuke dag te zorgen voor mij, ik kom zorgen dat die mensen een leuke dag hebben.

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Chapter 3

Factors related to psychotropic drug prescription for neuropsychiatric symptoms in nursing home residents with dementia

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Claudia H.W. Smeets

Martin Smalbrugge

Sytse U. Zuidema

Els Derksen

Erica de Vries

Klaas van der Spek

Raymond T.C.M. Koopmans

Debby L. Gerritsen

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Abstract

Objectives: The objective of this study is to explore factors that elucidate reasons for psychotropic drug (PD) prescription for neuropsychiatric symptoms (NPS) in nursing home (NH) residents with dementia.

Design: A qualitative study using a grounded theory approach.

Setting: Twelve NHs in the Netherlands.

Participants: Fifteen physicians and fourteen nurses.

Measurements: Individual, face-to-face, in-depth semi-structured interviews. Interviews were audio recorded, transcribed, and qualitatively analyzed using Atlas.ti.

Results: The qualitative analysis revealed four emerging themes with factors either or both enhancing or limiting PD prescription, which we used to develop a conceptual framework. First, the mindset of physicians and nurses towards NPS and PDs appeared to contribute. Second, inadequate knowledge of and experience with NPS and limited people skills of nurses may induce PD prescription. Also, knowledge of effectiveness and side effects of PDs from education, literature, and guidelines, and previous personal experiences was considered relevant. Third, effective communication and cooperation between professionals and with family may improve the appropriateness of PD prescription. Fourth, external factors including staffing issues, nursing home setting, access to consultants, national and local policies, and *zeitgeist* were considered to affect PD prescription.

Conclusion: We have developed a conceptual framework explaining how different factors influence PD prescription. This provides opportunities for improving PD prescription in NH residents with dementia.

Introduction

Neuropsychiatric symptoms (NPS) occur frequently in people with dementia. These symptoms, which can be divided into psychiatric symptoms (delusions, hallucinations, depressive symptoms, anxiety, euphoria) and behavioral symptoms (agitation, aggression, apathy, disinhibition), have prevalence-rates of about 80% in nursing home (NH) residents with dementia [1]. NPS are burdening for both residents and caregivers, and severely affect residents' quality of life [2]. Despite the availability of psychosocial interventions, NPS are frequently treated with psychotropic drugs (PDs) that have limited effectiveness and carry a risk of considerable side effects such as extrapyramidal symptoms, somnolence, dehydration, and increased risk on falls, stroke, and mortality [3, 4]. This raises the question of why 52 to 80% of NH residents with dementia still use PDs [5-9]. The optimization of PD prescription for NPS has recently attracted considerable attention and debate [10-13]. In order to improve prescription, it is crucial to identify the factors related to the prescription of PDs for NPS.

Literature reveals that various patient- and environment-related factors influence the prescription of PDs for NPS in NH residents with dementia. Factors enhancing PD prescription are: NPS [6, 7, 14-16], psychiatric disorders [15, 16], admission from another institution[16], and high staff distress because of resident's agitation [6]. Factors limiting PD prescription are: presence of comorbidity [16], final phase of dementia [17], and a higher staff/resident ratio [6]. Risk factors with inconsistent association are sex [7, 15], age [7, 14, 16], level of care dependency [7, 15], and number of beds per institution [15]. Our previous study examining the contribution of several patient and environmental risk factors was able to explain only 20% of the variance of PD prescription in NH residents with dementia [6].

Whereas quantitative studies are able to detect the presence and relevance of hypothesized factors related to PD prescription, qualitative studies may elucidate new factors and identify why and how factors contribute. However, only a limited number of qualitative studies have been conducted in this area. In these studies, the following factors were found to be most relevant: expected benefits of PDs for NPS, sporadic occurrence of side effects, pressure on physicians by nurses or family to start PDs, and lack of resources, staff training, and feasible alternatives [18-20]. Because PD prescription is a multidisciplinary process, it appears important to include both physicians and nurses in qualitative studies. Of the studies mentioned above, one included only psychiatrists [19] whereas the other two were based upon surveys with a focus on nonpharmacological interventions [20] and on antipsychotics [18]. What to our best knowledge is not yet fully explored in depth, is the opinion of nurses on why and how they think that factors contribute to prescription, and the ideas of both physicians and nurses on not only antipsychotics or alternatives of PDs, but on all types of PDs. Knowing why and how factors contribute to prescription, will help identifying factors to be targeted for improving the appropriateness of PD prescription in daily practice, but also to be studied in future quantitative research.

To further explore factors elucidating PD prescription, we performed a qualitative study using the principles of grounded theory. We focused on all PDs and interviewed not only physicians who regularly prescribe PDs, but also nurses who deal with NPS daily.

Methods

Design and setting

This study is part of the mixed methods PROPER (PRescription Optimization of Psychotropic drugs in Elderly nuRsing home patients with dementia) I study, which aims to study prevalence and appropriateness of PD prescription and to understand factors associated with PD prescription in twelve Dutch NHs [21]. We applied a grounded theory [22] approach by interviewing physicians and nurses treating and caring daily for people with dementia. In the Nether-lands, people with progressed dementia usually reside in dementia special care units (SCUs). Care is provided by physicians, mostly elderly care physicians [23], and nurses. Nursing education is divided into five levels, which we con-sider comparable with nursing assistant (level 1 and 2), certified nursing assistant (level 3), and registered nurse (level 4 and 5). From the participating SCUs involved in the parallel quantitative study, we included all physicians and a selection of one or two nurses specifically assigned to individual residents.

Ethics

The study was rated by the local Medical Ethics Review Committee 'CMO Regio Arnhem-Nijmegen' (number 2011/ 033), which stated that the study was not subject to the Medical Research Involving Human Subjects Act. NH management boards gave permission for the study, which was conducted in accordance with the Declaration of Helsinki [24]. All participants verbally consented with participation and with audio recording of the interview, which was analyzed using unique and anonymous codes.

Data collection

An initial topic list was developed based upon consultation of experts with clinical experience and knowledge of the literature in NH research; it was then pilot tested. We conducted and audio recorded individual, face-to-face interviews at each of the participating NHs. The interviewers were two psychologists (EV, KS) and one medical biologist (CS). After an introduction, the interview started with a general question: "What occurs to you when thinking about PDs prescribed to residents with dementia?" Depending on the participant's answers, additional questions were asked about one or more of the following topics: the standard practice of prescription, the participant's own opinion, colleagues' opinions, family's opinions, current prescription practices compared with those in the past, influences of the NH, opinions on the best solutions for NPS in dementia, and ideas about the influence of politics and media attention. Interviews were identified by labeling with a letter-number combination. Demographic data on profession, sex, and age were collected electronically.

Data analysis

Directly upon interviewing, we conducted a preliminary analysis: audio recorded interviews were listened to and analyzed concisely by EV. Then, feedback was shared between the three interviewers in order to identify potentially interesting additional topics or topics that seemed to require further in-depth exploration. The topic list was therefore repeatedly extended throughout the interview period with the following (sub)topics: withdrawal of PDs, PD prescription before NH admission, pressure to prescribe, guidelines for prescription, stakeholders who benefit from PDs, and role of education. All interviews were transcribed *ad verbatim* and transcriptions were cross-checked with the recordings afterward. We used a strategy that can be described as 'retrospective purposive sampling' by selecting the interviews for detailed analysis based upon profession, sex, age, experience, location, and interviewer. Data analysis was an iterative process involving several steps. We started by open coding to identify factors using Atlas.ti software version 7.1.5 (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany). Initially, two researchers coded independently until consensus was reached. Subsequently, two researchers independently performed axial coding and discussed factors and themes until consensus was reached and a conceptual framework describing all factors and their connections emerged. We used constant comparative analysis [22] by continued coding and refining the framework until no new information could be added and the stage of conceptual saturation was reached.

Validity, reliability, bias

In order to limit bias and ensure reliability, two researchers conducted the analysis (CS, EV) and had repeated group discussions with three other researchers with expertise in the field of dementia in NHs (DG, MS, ED).

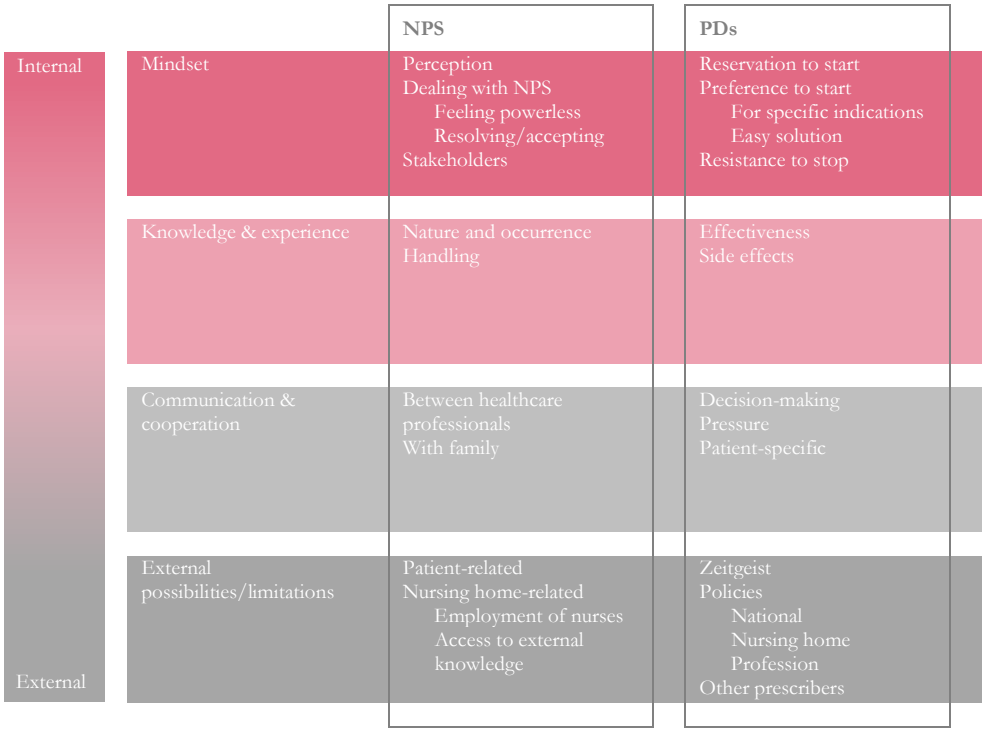
Results

We analyzed interviews from fifteen physicians and fourteen nurses. Most of the physicians were elderly care physicians; one was a resident in elderly care medicine and one a medical doctor. Ten were female and five male with a mean age of 47 years (range 29 to 65). Of the nurses, four were registered nurses, nine were certified nurse assistants, and one was a nurse assistant. Nurses were all female with a mean age of 37 years (range 24 to 52). Interviews had an average duration of one-half of an hour. In the results presented below, we use 'participants' if both physicians and nurses reported findings. Otherwise, we specify whether a factor was mentioned by either physicians or nurses exclusively.

The analysis resulted in four emerging themes thought to contribute to the start and continuation of PDs. The first theme '*mindset*' comprises personal feelings, ideas, and attitudes that were considered to reflect personality, subjective (religious) beliefs and personal characteristics of both physicians and nurses. The second theme '*knowledge & experience*' includes factors with

respect to knowledge as well as experience such as level of training and number of years of employment. The third theme '*communication & collaboration*' covers all interactions between physicians, nurses, other professionals, and family. The quality and level of communication and cooperation – including openness, addressing topics for discussion, sharing knowledge and ideas – appears to affect whether or not PDs are prescribed. The fourth theme '*external possibilities/limitations*' comprises factors on the community level. These four themes can be scaled from internal to external, resulting in a hypothetical framework starting with the most internal *mindset* (i.e., personal/in close proximity to the individual), and progressing, as environmental influences increase, toward *external possibilities/limitations*. All four themes are closely related and interconnected. The discussion of PDs extended in all interviews to NPS, which we address as the subtheme 'NPS' next to the subtheme 'PDs' (Figure 1).

Figure 1. Conceptual framework of factors related to PD prescription for NPS in NH residents with dementia.



Mindset

Mindset regarding NPS

Perception of NPS plays an important role in the prescription of PDs: the intensity or even presence to label symptoms as NPS appears to be subjective, especially between nurses.

> *And what is restless? What restless is for me, is not always the same for a colleague. (Nurse 16)*

Nurses also indicated that the perception of NPS is influenced by taking NPS personally. In addition, dealing with NPS plays an important role: feeling helpless toward NPS provokes PD prescription.

> *I mean . . . we try to do a lot, but sometimes you've got your back against the wall and you have such a restless patient that you simply have no other choice than to prescribe medication. (Physician 5)*

Feeling helpless seems to be related to the nature of NPS: it appears that starting PDs for aggression is considered more reasonable than for other indications. In contrast, dealing with NPS either by resolving underlying causes or accepting NPS prevents PD prescription. Also, it seemed to be relevant which specific stakeholder (resident him/ herself, nurses, family, or other residents) perceives the NPS as too troublesome.

> *In some cases the person is suffering so much, and other residents may be suffering or in danger as a result. Then, I think it is appropriate to prescribe. (Physician 8)*

Physicians reported not always having a clear view in the interest of whom of the above-mentioned stakeholders the PDs are actually being prescribed.

Mindset regarding PDs

Reservation was the main mindset expressed by participants, with both physicians and nurses reluctant to start the prescription of PDs.

> *The first thing that crosses my mind is as little psychotropics as possible in dementia. Only if there is really no other way. [. . .] As little as possible, and first try to influence the behavior by exhausting all other interventions. [. . .] Without medication you can solve a lot. A lot. And you should do that first. (Physician 19)*

When prescribing is unavoidable, physicians feel it should be done with careful consideration, evaluation, and, over time, dose reduction or stopping entirely. They consider PD prescription more acceptable when applied as co-treatment alongside psychosocial interventions. However, participants also mentioned that PDs are justified in certain situations and even appropriate for specific indications such as depression or hallucinations. Participants thought that PDs are also

seen as an easy solution for NPS, especially for nurses believing in the effectiveness of PDs and the NPS are - either or not due to PDs - no longer perceived as too troublesome, there is a preference to continue. There can even be resistance from nurses and family to withdraw PDs, especially when considerable effort was put into stabilizing the NPS.

> *Because you simply are afraid that the same behavior will come back. And at that moment, you are actually glad someone is doing well. And then you think like, gosh, should you take the risk to – so to say – stop and see the problems return? (Physician12)*

Knowledge and experience

Knowledge and experience regarding NPS

Participants saw a clear relationship between knowledge and experience, primarily of nursing staff, and the need for PDs. There seems to be a greater need for PDs in cases where nurses have limited knowledge – either or not from formal education – on the nature and occurrence of NPS or less experience in managing NPS.

> *I think [. . .] that there is a very hesitant reaction to problem behavior by the nursing staff. That in general there is little knowledge and few skills related to dementia and types of dementia. Thus the reason it is often perceived as difficult.* (*Physician 3)*

Knowledge and experience regarding PDs

PD knowledge and experience was also considered relevant. This includes not only knowledge on effectiveness of individual PDs for certain indications from education, literature and guidelines, but also previous personal prescribing experiences with PDs. Unfounded high expectations on effectiveness by nurses or family, and inadequate knowledge of dosing mechanisms by nurses may induce (additional) PD prescription. Physicians with limited work experience appear reluctant to start PDs and to stop previously prescribed PDs. Additional reluctance may result from limited knowledge in the public field: on the mechanism of action of PDs, lack of data on PDs in the NH population, and the impression that trials are selective and test only PDs in the business interests of pharmaceutical companies. In addition, participants mentioned that positive effects as experienced in individual cases might encourage PD prescription, despite limited effectiveness according to evidence-based medicine. Participants consistently estimated the side effects of PDs to be considerable and therefore a reason for reluctance to prescribe.

> *Those are often nasty pills because they have side effects; people get drowsy. And [. . .] making patients drowsy is actually something that you have to check carefully. The most important thing that a dementia patient has is his consciousness; being able to interact with the environment. And when you subdue that with medication, I don't find that to be good medicine. (Physician 13)*

Communication and cooperation

Communication and cooperation regarding NPS

Participants felt that effective communication and cooperation between professionals may prevent occurrence or escalation of NPS, thereby avoiding the need for prescription of PDs.

> *At a certain moment we started having some kind of meetings [. . .] purely to discuss the residents. [. . .] By jointly looking at the problems and by learning from each other [. . .] we gained more clarity, much more peace, and also had a significant decrease in prescribed medication. (Physician12)*

This also applies to communication between NH personnel and family, because the latter usually knows residents' preferences, wishes and needs, which may help in prevention or management of NPS. Both nurses and physicians emphasized the importance of clear reporting by nurses of occurrence and severity of NPS, since physicians mostly use this as a base to decide on starting PDs.

> *Look, a physician does not see the residents, I see them all day long. We, altogether, see a resident twenty-four hours per day, so if we accurately register their behavior, then . . . The physician is very reliant upon us. (Nurse 15)*

Physicians assumed that the cooperation between nurses, physicians, and psychologists with respect to observation of NPS and approaching residents in the correct manner might help limit the need for PDs.

Communication and cooperation regarding PDs

Communication and cooperation regarding PDs appeared crucial in the process of decision-making. This includes weighing the effectiveness of a medication against its side effects, and balancing the interests of different stakeholders. Participants mentioned that the physician occasionally needs to convince the family, but that the family usually follows the physician's advice with respect to prescription. In addition, physicians reported sometimes feeling pressured by nurses and, to a lesser extent, by family members to start prescribing PDs.

> *That gentleman is so restless and they are all getting crazy and something must happen, NOW. That is how it goes. (Physician 19)*

In contrast, some nurses indicated putting pressure on physicians not to start PDs. Physicians also emphasized the importance of communicating with the family about resident-specific PD experiences.

I have experienced that the family said something like, "Yes . . . in the past, dad or mom used to have the same and then this or that agent was prescribed and [. . .] that only makes it worse." Then I say, "Thank you, we will try something different." (Physician 7)

External possibilities/limitations

External possibilities/limitations regarding NPS

Participants thought that despite efforts to reduce PD prescription by treating or eliminating the cause of NPS, or by applying alternative treatments, NPS and subsequently the need for PDs will always exist. Changes in the NH population were considered to play a role, since people with dementia tend to stay at home longer, and that people with more severe dementia at admission consequently have more NPS. They also assumed that NPS decrease in the final phase of dementia, meaning that PDs can be stopped then. Additionally, participants thought that the need for PDs is related to the NH setting itself: the occurrence of NPS will always be higher than at home since NPS are a common reason for admission, and commotion within the NH setting may even provoke NPS. They also considered the process of NH admission an emotional event potentially causing NPS. Moreover, participants mentioned several staffing issues that potentially lead to increased PD prescription. First, it was felt that the number of nurses or other personnel was insufficient to spend enough time with residents for giving real attention, and providing distraction and activities. Nurses estimated that this affects the need for PDs, especially at sundown and during night shifts.

If everyone would have one-on-one care, the problem behavior might become something of the past. (Physician15)

Second, the employment of temporary nurses was felt to affect continuity in care and relationships with the residents. Third, the employment of lower educated nurses was considered significant.

The level that is put in is getting lower, while we know that there is a gigantic lack of knowledge. There would be much more benefit with levels four and five, but that is too expensive. (Physician 3)

Fourth, the employment of nurses with limited people skills and lack of flexibility to deviate from rules or protocols was thought to induce PD prescription. Moreover, participants considered limited access to consultants such as psychologists or old age psychiatrists as an aspect enhancing the need for PDs.

External possibilities/limitations regarding PDs

Participants thought the public tends toward critical scrutiny, which possibly leads to a withdrawal of PDs; they assumed that the *zeitgeist* favors limiting the prescription of PDs.

Personally, I have the feeling that the tendency is to prescribe less PDs and less quickly. As little as possible, actually; the less the better. This is, in my opinion, also something of my generation. (Physician 4)

According to the physicians, this is consistent with the national policy of the Dutch Health Care Inspectorate, as well as with local NH policies. PD prescription is posed as a quality indicator for NHs, which consequently stimulates the NH sector to reduce prescription.

[Name of institution] also prefers to have as little as possible. So we are working on that more actively, it also makes you more aware, of course. (Nurse 10)

Physicians expressed ambivalence about the influence of the Dutch professional guideline. According to some, it limits PD prescription; others believe that when followed routinely and interpreted as "allowance" to prescribe PDs, it stimulates prescription. Finally, physicians indicated that PDs initiated by other prescribers (in urgent situations during night or weekend shifts, or by general practitioners prior to NH admission) are too easily continued.

Discussion

Our study focuses on explaining PD prescription, and is based upon the qualitative analysis of interviews with physicians and nurses. It elucidates four main themes: *mindset*, *knowledge & experience*, *communication & collaboration*, and *external possibilities/limitations*. The themes are interconnected and range from more personal toward environmental.

Comparing our results with the literature, we found many patient- and environment-related factors that were also reported in the studies by Cohen-Mansfield et al [20], Wood-Mitchell et al. [19], and Cornegé-Blokland et al. [18] However, we found that about one quarter of our factors were connected in an overarching theme, which we called *mindset*. Although some of these factors such as accepting/having a threshold toward NPS, resolving underlying causes of NPS, PDs as an easy solution, and the need for evaluation of PDs [19, 20] were previously identified, we discovered within this theme several additional factors either provoking or limiting PD prescription. Provoking factors were: the preference to continue PDs in cases where the resident's NPS was stable; the difficulty nurses had accepting NPS, because they can take the NPS personally; the acceptability of prescribing PDs in addition to another intervention; and, the use of PDs in order to avoid the escalation of NPS to other residents. A factor limiting PD prescription was the mindset that NPS also disappear without PDs. In the theme *knowledge & experience*, the factor 'limited experience of physicians to dare starting or discontinuing PDs' seems not to be described previously. In the theme *external possibilities/limitations*, we also found new inducing factors: a short employment span of nurses, the perceived stimulation by the profession to prescribe PDs; and we found a limiting factor: the *zeitgeist*. Among these newly

identified factors, several are specifically related to the continuation of previously initiated PDs, a subject that has not, to the best of our knowledge, been addressed in the literature so far.

Limitations

The study has some limitations. In line with the PROPER I study, we focused on the perspectives of physicians and nurses involved in PD prescription. If we had been able to conduct the in-depth analysis directly upon interviewing, we might have identified other stakeholders earlier as a valuable addition – especially family. Furthermore, it would have been interesting to differentiate between PD classes to find out whether factors were specifically related to certain PD classes. Moreover, the study was conducted in the Netherlands, within the specific setting of SCUs and with a majority of physicians being educated as elderly care physicians. Interviewing healthcare professionals from other countries might have yielded different results.

Practical implications

Although the presence and relevance of factors within our conceptual framework needs to be verified in quantitative studies, our results offer preliminary recommendations for improvement of PD prescription in the daily nursing home setting. First, interventions for changing the mindset toward NPS and PDs may be useful. This is in line with a recent study by Lemay et al. concluding that education on antipsychotics should target not only knowledge but also beliefs [25]. Second, education may have the potential to enhance nurses' awareness of side effects and limited efficacy and thereby reduce their requests for PD prescription. This may also hold true for education of physicians in the prescription of PDs, which could increase their assertiveness toward pressure to prescribe PDs and teach them how to deal with situations that evoke feelings of helplessness. Third, improving communication is another starting point for improving PD prescription. Communication and cooperation between nurses with regard to the occurrence and treatment of NPS, but also between nurses and physicians to clearly outline and objectify the severity of NPS, appear to be subjects for improvement. Also, improvement of quality of communication with the family may help in reducing the need for PDs due to their resident-specific knowledge of occurrence and treatment of NPS. Fourth, there may be an opportunity for improvements at the NH level, especially with regard to hiring adequate numbers of psychologists for advice in the approach of residents and sufficiently educated and skilled nurses for long-term employment. Finally, paying more attention to the opportunity to stop previously started PDs may also improve PD prescription.

Conclusion

By qualitative exploration, we have developed a conceptual framework explaining how different interconnected factors influence PD prescription. It revealed factors that may be targeted when improving PD prescription in NH residents with dementia. Additionally, by incorporating these insights into quantitative research on PD prescription, knowledge about underlying mechanisms explaining and improving PD prescription can be advanced even further.

References

1. Selbaek, G., K. Engedal, and S. Bergh, *The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: a systematic review.* J Am Med Dir Assoc, 2013. **14**(3): p. 161-9.
2. Wetzels, R.B., et al., *Determinants of quality of life in nursing home residents with dementia.* Dement Geriatr Cogn Disord, 2010. **29**(3): p. 189-97.
3. Ballard, C.G., et al., *Management of agitation and aggression associated with Alzheimer disease.* Nat Rev Neurol, 2009. **5**(5): p. 245-55.
4. Seitz, D.P., et al., *Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic review.* Int Psychogeriatr, 2013. **25**(2): p. 185-203.
5. Wetzels, R.B., et al., *Prescribing pattern of psychotropic drugs in nursing home residents with dementia.* Int Psychogeriatr, 2011. **23**(8): p. 1249-59.
6. Zuidema, S.U., et al., *Psychotropic drug prescription in nursing home patients with dementia: influence of environmental correlates and staff distress on physicians' prescription behavior.* Int Psychogeriatr, 2011. **23**(10): p. 1632-9.
7. Richter, T., et al., *Prevalence of psychotropic medication use among German and Austrian nursing home residents: a comparison of 3 cohorts.* J Am Med Dir Assoc, 2012. **13**(2): p. 187 e7-187 e13.
8. Hosia-Randell, H. and K. Pitkala, *Use of psychotropic drugs in elderly nursing home residents with and without dementia in Helsinki, Finland.* Drugs Aging, 2005. **22**(9): p. 793-800.
9. Kim, H. and A.L. Whall, *Factors associated with psychotropic drug usage among nursing home residents with dementia.* Nurs Res, 2006. **55**(4): p. 252-8.
10. Morley, J.E., *Dementia-related agitation.* J Am Med Dir Assoc, 2011. **12**(9): p. 611-612 e2.
11. Rapp, M.A., et al., *Agitation in Nursing Home Residents With Dementia (VIDEANT Trial): Effects of a Cluster-Randomized, Controlled, Guideline Implementation Trial.* J Am Med Dir Assoc, 2013. **14**(9): p. 690-5.
12. Blazer, D.G., *Antipsychotics and dementia: where do we go from here?* J Am Med Dir Assoc, 2013. **14**(4): p. 307-8.
13. Volicer, L., *Antipsychotics do not have to be used "off label" in dementia.* J Am Med Dir Assoc, 2012. **13**(6): p. 495-6.
14. Nijk, R.M., S.U. Zuidema, and R.T. Koopmans, *Prevalence and correlates of psychotropic drug use in Dutch nursing-home patients with dementia.* Int Psychogeriatr, 2009. **21**(3): p. 485-93.
15. Kamble, P., et al., *Use of antipsychotics among elderly nursing home residents with dementia in the US: an analysis of National Survey Data.* Drugs Aging, 2009. **26**(6): p. 483-92.
16. Larrayadieu, A., et al., *Associated factors with antipsychotic use in assisted living facilities: a cross-sectional study of 4367 residents.* Age Ageing, 2011. **40**(3): p. 368-75.
17. Blass, D.M., et al., *Medication use in nursing home residents with advanced dementia.* Int J Geriatr Psychiatry, 2008. **23**(5): p. 490-6.

18. Cornege-Blokland, E., et al., *Reasons to prescribe antipsychotics for the behavioral symptoms of dementia: a survey in Dutch nursing homes among physicians, nurses, and family caregivers.* J Am Med Dir Assoc, 2012. **13**(1): p. 80 e1-6.
19. Wood-Mitchell, A., et al., *Factors influencing the prescribing of medications by old age psychiatrists for behavioural and psychological symptoms of dementia: a qualitative study.* Age Ageing, 2008. **37**(5): p. 547-52.
20. Cohen-Mansfield, J., et al., *Wisdom from the front lines: clinicians' descriptions of treating agitation in the nursing home, a pilot study.* J Am Med Dir Assoc, 2005. **6**(4): p. 257-64.
21. van der Spek, K., et al., *PROPER I: frequency and appropriateness of psychotropic drugs use in nursing home patients and its associations: a study protocol.* BMC Psychiatry, 2013. **13**(1): p. 307.
22. Corbin, J. and A. Strauss, *Grounded theory research: Procedures, canons, and evaluative criteria.* Qualitative Sociology, 1990. **13**(1): p. 3-21.
23. Koopmans, R.T., et al., *Dutch elderly care physician: a new generation of nursing home physician specialists.* J Am Geriatr Soc, 2010. **58**(9): p. 1807-9.
24. World Medical Association, *Declaration of Helsinki: ethical principles for medical research involving human subjects.* JAMA, 2013. **310**(20): p. 2191-4.
25. Lemay, C.A., et al., *Knowledge of and perceived need for evidence-based education about antipsychotic medications among nursing home leadership and staff.* J Am Med Dir Assoc, 2013. **14**(12): p. 895-900.

Arts: En de verzorgenden, hun vraag is vaak uit nood geboren. [...] De meesten hebben ook wel in de smiezen dat wanneer iemand onrustig is, dat dat heel erg onaangenaam is [...] voor die bewoner, anders deed hij niet zo raar. Dat doet hij niet om de verzorgenden te pesten.

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Chapter 4

Psychotropic drug prescription for nursing home residents with dementia: prevalence and associations with non-resident-related factors

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Claudia H.W. Smeets

Debby L. Gerritsen

Sytse U. Zuidema

Steven Teerenstra

Klaas van der Spek

Martin Smalbrugge

Raymond T.C.M. Koopmans

Abstract

Objectives: To determine psychotropic drug prescription rates in nursing home residents with dementia and to identify associations with the so far understudied psychosocial non-resident-related factors.

Method: A cross-sectional, observational, exploratory design as part of PROPER I (PRescription Optimization of Psychotropic drugs in Elderly nuRsing home patients with dementia). Participants were 559 nursing home residents with dementia, 25 physicians, and 112 nurses in the Netherlands. Psychotropic drug prescription, non-resident-related and known resident-related variables were measured to operationalize the themes of our previous qualitative analysis.

Results: Fifty-six percent of residents were prescribed any psychotropic drug, 25% antipsychotics, 29% antidepressants, 15% anxiolytics, and 13% hypnotics, with large differences between the units. Multivariate multilevel regression analyses revealed that antipsychotic prescription was less likely with higher physicians' availability (odds ratio 0.96, 95% confidence interval 0.93-1.00) and that antidepressant prescription was more likely with higher satisfaction of nurses on resident contact (odds ratio 1.50, 95% confidence interval 1.00-2.25). Resident-related factors explained 6%-15% of the variance, resident- and non-resident-related factors together 8%-17%, depending on class of drugs.

Conclusion: Prescription rates for antipsychotics are similar compared to other countries, and relatively low for antidepressants, anxiolytics and hypnotics. Our findings indicate that improvement of prescribing could provisionally best be targeted at resident-related factors.

Introduction

Although psychotropic drugs (PDs) have only modest efficacy for treatment of neuropsychiatric symptoms (NPS), and can cause severe side effects [1-7], these agents are widely prescribed in nursing home residents with dementia. Worldwide, 66% to 79% of nursing home residents are treated with any PD, 12% to 54% with antipsychotics (APs), 28% to 40% with antidepressants (ADs), 16% to 29% with anxiolytics and 15% to 23% with hypnotics [8-13]. In order to optimize prescription, it is relevant to be aware of the current prescription rates, and it is of major importance to know the correlates of PD prescription, so that those susceptible to change can be improved.

Several factors contributing to PD prescription have been investigated, the most extensive of which were the resident-related factors. In general, more severe NPS [9, 12, 14-18], comorbid psychiatric disorders [18-20], and less severe stage of dementia [14, 21] are associated with higher prescription rates. Non-resident-related factors are increasingly being recognized as potential correlates. Higher staff distress due to residents' agitation [13] and factors such as a larger facility [17], lower staff/resident ratio [13, 22, 23], and lower resident satisfaction of number of staff, of personal care, and of recreational activities [17] are related to higher PD prescription. Also qualitative studies, have sought to elucidate additional factors [24-27] and underpinned the need to explore the prescribing culture [28]. These studies point at an important share of psychosocial non-resident-related factors, including feeling powerless toward NPS, previous prescribing experiences of physicians, communication among professionals and with family, educational level of nurses, nursing home staffing and continuity in care. So far, these psychosocial factors have to our best knowledge not been quantitatively studied. This study aims to obtain insight into current prescription rates and to identify the so far understudied psychosocial non-resident-related factors.

Methods

Design and setting

This exploratory study is part of PROPER I [29]. It has a cross-sectional, observational design and was conducted between January and July 2012 in Dutch nursing homes. In the Netherlands, nursing home locations are usually part of larger long-term care organizations with specific dementia special care units (DSCUs). DSCUs can be either small- (5 to 10 residents) or regular-scale (10 to 30 residents). Primary responsible nurses are assigned to individual residents, and physicians, mainly certified as elderly care physician, are employed by the nursing home [30]. We aimed for a sample size of 540 residents with dementia, with maximum contrast in prescription rates, and their nurses and physicians [29]. Therefore, we selected DSCUs based upon PD prescription rates as reported in questionnaires previously distributed among all Dutch elderly care physicians.

The local Medical Ethics Review Committee 'CMO Regio Arnhem-Nijmegen' rated the study [number 2012/226] and stated that it was in accordance with the applicable Dutch rules concerning review of research ethics committees and informed consent. The study was conducted in accordance with the Declaration of Helsinki [31].

Measures

Table 1 shows all measures included in this study.

Table 1. All measures included in this study.

Dependent variables
Psychotropic drug prescription
Independent variables
Resident-related factors
Age of resident
Sex of resident
Length of stay at DSCU
Dementia type
NPI-Q Severity
CMAI
Non-resident-related factors
Mindset
NPI-Q Emotional distress
SDCS
MAS-GZ subscale 'satisfaction of resident contact'
ADQ (physician)
ADQ (nurse)
Knowledge and experience
Profession (nurse)
Number of years employed at DSCU (nurse)
Number of years working as physician
Number of months working at DSCU (physician)
Communication and cooperation
MAS-GZ subscale 'satisfaction of colleague contact'
MAS-GZ subscale 'satisfaction of clarity'
External possibilities/limitations
Work Stress Scale
CVFS
Nurse/resident ratio during day
Nurse/resident ratio during night
Physicians' availability per resident
Number of residents per DSCU
Number of different caregivers at DSCU

DSCU: dementia special care unit, NPI-Q: Neuropsychiatric Inventory Questionnaire, CMAI: Cohen-Mansfield Agitation Inventory, SDCS: Strain in Dementia Care Scale, MAS-GZ: Maastricht Work Satisfaction Scale for Healthcare, ADQ: Approaches to Dementia Questionnaire, CVFS: Competing Values Framework Scale.

Dependent variables

PD prescription was grouped according to the Anatomical Therapeutic Chemical (ATC) classification into: APs (N05A), ADs (N06A), anxiolytics (N05B), and hypnotics (N05C) [32]. PD prescription was measured as PD prescription at the day of assessment for treatment of NPS explained by the presence of a dementia, a sleep disorder or a delirium, and excluding pro re nata use. The maximum time window between use of PDs and possibly related factors was 6 weeks.

Independent variables

Selection of measures. For operationalization of non-resident-related factors, we used results of the previously conducted qualitative analysis of the PROPER I study [27]. We opted to analyze specifically those (sub)scales among the quantitative data, fitting in the four themes contributing to PD prescription, after critical review and consensus among the co-authors: 1) *mindset*, e.g. perceptions and opinions of physicians and nurses toward the nature and intensity of NPS and toward PDs, 2) *knowledge and experience* of physicians and nurses with regard to NPS and PDs, such as level of training and number of years of employment, 3) effective *communication and collaboration* among healthcare professionals regarding NPS and PDs, and 4) *external possibilities/ limitations*, comprising staffing issues, like sufficient time for the job, number and continuity of nurses, and issues related to living within a nursing home setting. This led to the exclusion of variables regarding the use of psychosocial interventions, physical environment, and satisfaction of career perspective, of quality of care, and of unit supervisor. We also included known resident-related variables. Moreover, the qualitative results indicated that factors differ per class of PD, which compelled us to study AP, AD, anxiolytics, and hypnotics separately.

Resident-related factors. We collected data on age, sex, length of stay at DSCU and chart diagnosis of dementia as categorized into Alzheimer's dementia, vascular dementia, mixed Alzheimer's/vascular dementia, and other dementia (including 'not otherwise specified').

We assessed the severity of NPS using the 12-item Neuropsychiatric Inventory Questionnaire (NPI-Q) [33, 34]. Symptoms were grouped into clinically meaningful clusters or individual symptoms, similar to this instrument's Nursing Home version [13]. From these, we included only those that were potential indications for a specific class of PDs [35]. For AP: psychosis (range 0 to 6, a higher score reflecting higher severity), agitation (range 0 to 9), and nighttime behavior (range 0 to 3); for AD: agitation, depression (range 0 to 3), anxiety (range 0 to 3); for anxiolytics: agitation and anxiety; and for hypnotics: anxiety and nighttime behavior. NPS were also assessed using the Cohen-Mansfield Agitation Inventory (CMAI) [36, 37], consisting of 29 agitated behaviors, which we grouped into three clusters: physical aggression (range 8 to 56, a higher score reflecting more frequent occurrence), physically nonaggressive behavior (range 7 to 49), and verbally agitated behavior (range 4 to 28) [37]. Also for the CMAI, we included only

clusters that were potential indications: all three CMAI clusters for AP, physical aggression and verbally agitated behavior for AD and for anxiolytics, and none for hypnotics.

Non-resident-related factors. To operationalize nurses' perceptions and opinions, the *mindset*, we used four measures. The first was the NPI-Q emotional distress scale which assesses distress caused by NPS, according to the aforementioned clusters. This resulted in following ranges (higher score reflecting higher distress): 0 to 10 for psychosis, 0 to 15 for agitation, and 0 to 5 for depression, anxiety, and nighttime behavior. The second was the 27-item Strain in Dementia Care Scale (SDCS) [38] that measures nurses' feelings with regard to caring for residents with dementia (range 1 to 16, a higher score reflecting higher distress). The third measure was the subscale 'satisfaction of resident contact' from the Maastricht Work Satisfaction Scale for Healthcare (MAS-GZ) [39], consisting of three items on mutual liking between residents and nurses (range 1 to 5, a higher score indicating higher satisfaction). The fourth was the 19-item Approaches to Dementia Questionnaire (ADQ) , which measures the attitude toward caring for people with dementia [40] (range 19 to 95, with a higher score reflecting more positive attitude). To operationalize the *mindset* of physicians, we also used the ADQ.

For operationalization of nurses' *knowledge and experience*, we used their profession, categorized into nursing assistant, certified nursing assistant, or registered nurse, and the number of years employed at the current DSCU. For physicians, we used number of years working as a physician, and number of months working at the current DSCU.

We used two other MAS-GZ subscales to operationalize nurses' *communication and cooperation*: 'satisfaction of colleague contact', with items on mutual liking between nurses and colleagues, and 'satisfaction of clarity', with items regarding tasks in the job.

To assess staffing issues of nurses within the *external possibilities/limitations* theme, we used the 8-item Work Stress Scale, an instrument on psychological stressors within healthcare [41] (range 1 to 5, a higher score reflecting more stress). Moreover, we used the 6-item Competing Values Framework Scale (CVFS), which assesses dominance in four organizational cultures [42, 43]: clan (characterized by strong cohesion), adhocracy (which can adapt quickly to changes), hierarchy (with structure and rules), and market (result-oriented) (range 0 to 18, a lower score reflecting more dominancy). Furthermore, we used the nurse/resident ratio during the day (morning, afternoon, and evening) and during the night multiplied by 1,000 to allow interpretation of the odds ratios, and the physician's availability in minutes per resident per week. Finally, we used the number of residents per DSCU as a measure for commotion within the nursing home setting, and, for assessing continuity in care, the total number of different caregivers (e.g. nurses, supporting personnel) at the DSCU.

Procedures

Variables were either collected per individual resident (PD prescription, resident characteristics, NPI-Q and CMAI) or per group of residents (all other variables) [29]. Some data were retrieved by the researchers (PD prescription as documented in actual medication lists, resident characteristics (age, sex, length of stay at DSCU and diagnosis of dementia according to the patient's physician using DSM-IV criteria) as documented in patient's charts, and institutional characteristics (nurse/resident ratio, number of residents per DSCU, and number of different caregivers) as reported by the DSCU's team leader). All other data were collected web-based as completed per nurse or physician. For description of the population of physicians and nurses, we also asked them for their age and sex.

Statistical analyses

We conducted both univariate and multivariate multilevel logistic regression analyses with the prescription of APs, ADs, anxiolytics, and hypnotics separately as dependent variables. For the univariate analyses, variables were individually used as fixed effects, with the levels nursing home location and DSCU as random intercepts. In the multivariate modeling, we entered all independent variables per cluster for each of the five aforementioned clusters into a unilevel logistic regression model and applied stepward backward likelihood ratio selection with entry $p<0.05$, removal $p<0.10$, classification cut-off 0.5 and maximum 20 iterations. This resulted in a preselected set of resident-related and four sets of non-resident-related factors (*mindset*, and so on). Then, all variables from the five preselected sets were put together in a multilevel (resident within DSCU) logistic regression model.

In order to assess the robustness of our findings, we investigated whether and to which extent five alternative pathways for selecting variables into the final models led to different results: 1) without analyzing the cluster of resident-related factors; this was done to explore their influence; 2) by adding the clusters in a sequential order: first resident-related factors, then *mindset*, *knowledge and experience*, and so on, since factors in clusters earlier in this chain are thought to have a more direct influence than those of clusters later in this chain; 3) by using physicians instead of DSCU as level in model 2, to investigate if selection depended on the level of clustering; 4) by applying model 2 as a 3-level model (residents within DSCUs within nursing home locations), to investigate whether locations explained part of the variation; and 5) by entering the clusters in revised sequential order as applied in 4.

We used the Nagelkerke R^2 of the logistic regression models to estimate the amount of variance in PD prescription explained by the resident- and non-resident-related variables, and we used Pearson correlations to check for multicollinearity between severity and emotional distress of NPS. For all analyses, we used SPSS 22.0 (IBM, Armonk, NY).

Results

Prevalence rates

Participants were 559 residents, 25 physicians, and 112 nurses, distributed over 12 long-term care organizations, 21 nursing home locations, and 44 DSCUs, located throughout the Netherlands. Thirty-three percent of the residents had a chart diagnosis of Alzheimer's dementia, 17% of vascular dementia, 11% of mixed Alzheimer's/vascular dementia, and 39% of other/not otherwise specified dementia. Characteristics of the participants are shown in Table 2.

Table 2.

a. Characteristics of nursing home residents (N = 559)	
Mean age (years), [SD] (range)	84, [6.6] (62-100)
Sex, female N (%)	413 (74%)
Diagnosis of dementia, N (%)	
Alzheimer's dementia	186 (33%)
Vascular dementia	92 (17%)
Mixed Alzheimer's/vascular dementia	62 (11%)
Other dementia	219 (39%)
Length of stay at DSCU (months), [SD] (range)	23, [22.1] (0-118)
b. Characteristics of physicians (N = 25)	
Mean age (years), [SD] (range)	46, [11.2] (29-65)
Sex, female N (valid %)	16 (67%)
Current position, N (valid %)	
Elderly care physician	19 (79%)
Other physician	5 (21%)
Mean number of months working at DSCU, [SD] (range)	40, [29.3] (3-99)
Mean number of years working as physician, [SD] (range)	19, [12.3] (2-42)
c. Characteristics of nurses (N = 112)	
Mean age (years), [SD] (range)	43, [10.4] (22-61)
Sex, female N (valid %)	106 (98%)
Profession, N (valid %)	
Nursing assistant	10 (9%)
Certified nursing assistant	72 (67%)
Registered nurse	26 (24%)
Mean number of years working experience at current DSCU [SD] (range)	6.4, [6.3] (0-35)

SD: Standard Deviation, DSCU: dementia special care unit.

Prevalence of PD prescription was 56% for any PD, 25% for APs, 29% for ADs, 15% for anxiolytics, and 13% for hypnotics. Ranges varied: for any PD from 43 to 75% per nursing home location and from 33 to 88% per DSCU (see Table 3).

Table 3. Prevalence of psychotropic drug prescription (N = 559)

	Prevalence N (%)	Standard deviation (range)	
		per nursing home location	per DSCU
Psychotropics	311 (56%)	9.0 (43-75%)	13.1 (33-88%)
Antipsychotics	141 (25%)	14.5 (10-57%)	18.2 (0-62%)
Antidepressants	163 (29%)	11.5 (12-56%)	15.4 (0-75%)
Anxiolytics	85 (15%)	7.9 (0-31%)	12.8 (0-60%)
Hypnotics	74 (13%)	8.3 (0-27%)	11.9 (0-45%)

DSCU: dementia special care unit.

Correlates

This paragraph describes factors with statistically significant associations in both univariate and multivariate analyses according to the main model. The latter are also presented in Table 4. Full results are shown in the Appendices.

Resident-related factors

AP prescription was significantly more likely in the univariate analyses for residents with lower age, male sex, and more severe NPS (NPI-Q psychosis, agitation, depression, anxiety, nighttime behavior, and CMAI physical aggression, physically nonaggressive behavior, and verbally agitated behavior). In the multivariate model, AP prescription was more likely for longer stays at the DSCU and more severe NPS (CMAI physical aggression and physically nonaggressive behavior). Odds of AD prescription were higher in univariate analyses with more severe NPS (NPI-Q psychosis, agitation, depression and anxiety, and CMAI physical aggression and verbally agitated behavior). Anxiolytics prescription was more likely in the univariate analyses for residents with more severe NPS (NPI-Q anxiety and nighttime behavior, and CMAI physically nonaggressive behavior), and in the multivariate analyses with more severe NPS (NPI-Q anxiety). Hypnotics prescription was more likely in the univariate analyses for residents with more severe NPS (NPI-Q nighttime behavior and CMAI physically nonaggressive behavior).

Non-resident-related factors

From the *mindset* cluster, the odds of AP prescription were higher in the univariate analyses with higher emotional distress in nurses due to NPS (NPI-Q psychosis, agitation, depression, anxiety, and nighttime behavior). AD prescription was more likely in the univariate analyses with higher emotional distress due to NPS (NPI-Q agitation, depression, and anxiety), and in the multivariate analyses with higher nurses' satisfaction of patient contact (MAS-GZ). Odds of anxiolytics prescription were higher with higher emotional distress due to NPS (NPI-Q psychosis, agitation, anxiety, and nighttime behavior) in the univariate analyses. Hypnotics prescription was more likely with higher emotional distress due to NPS (NPI-Q nighttime behavior) in the univariate analyses. From the clusters *knowledge and experience* and *communication and cooperation*, none of the factors showed statistically significant relations, whereas from the *external possibilities/limitations cluster*, the multivariate analyses showed that AP prescription was less likely with a higher availability of the physicians.

Other results

Analysis results of the five alternative multivariate models were fairly consistent, with two exceptions for models 2 and 3: hypnotics prescription was less likely with a higher satisfaction of clarity regarding tasks in the job and with higher work stress.

The Nagelkerke R^2 showed that resident-related factors explained 6%-15% of the variance; resident-related and non-resident-related factors together explained 8%-17%. The total explained variance varied per class of PD: it was higher for AP and hypnotics (respectively 17% and 13%) than for AD and anxiolytics (both 8%).

The Pearson correlations between NPI-Q severity clusters/symptoms and their corresponding emotional distress NPI-Q clusters/symptoms were: 0.81 for psychosis, 0.84 for agitation, 0.78 for depression, 0.83 for anxiety, and 0.77 for nighttime behavior.

Table 4. Resident- and non-resident-related factors of psychotropic drug prescription in multivariate multilevel logistic regression analyses in 559 nursing home residents with dementia.

	AP OR (95% CI)	**AD** OR (95% CI)	**Anxiolytics** OR (95% CI)	**Hypnotics** OR (95% CI)
Resident-related factors				
Length of stay at DSCU	1.01 (1.00-1.02)	–	–	–
NPI-Q S anxiety	–	–	1.64 (1.16-2.30)	–
CMAI physical aggression	1.05 (1.00-1.09)	–	–	–
CMAI physically nonaggressive behavior	1.06 (1.03-1.09)	–	–	–
Non-resident-related factors				
Mindset				
MAS-GZ resident contact	–	1.50 (1.00-2.25)	–	–
Knowledge and experience	–	–	–	–
Communication and cooperation	–	–	–	–
External possibilities/limitations				
Physicians' availability per resident	0.96 (0.93-1.00)	–	–	–

AP: antipsychotics, AD: antidepressants, OR: odds ratio, CI: confidence interval, DSCU: dementia special care unit, NPI-Q S: Neuropsychiatric Inventory Questionnaire Severity, CMAI: Cohen-Mansfield Agitation Inventory, MAS-GZ: Maastricht Work Satisfaction Scale for Healthcare. Ranges: 0 to 3 for NPI-Q S anxiety, 8 to 56 for CMAI physical aggression, 7 to 49 for CMAI physically nonaggressive behavior, 1 to 5 for MAS-GZ. Only factors with statistically significant ORs are shown, full results are presented in the appendices. ORs are rounded on 2 decimal places, statistical significance is based upon the crude numbers.

Discussion

This study provides the latest Dutch PD prescription rates and is also the first exploratory study that quantitatively addresses the association of psychosocial non-resident-related factors with PD prescription. We found a relative absence of statistically significant associations, regardless of the statistical modeling strategy and class of PDs, and a very limited contribution to the explained variance, whereas the prevalence rates per nursing home location and DSCU varied considerably. These findings indicate that further improvement of PD prescription is very well possible.

Comparing the prevalence rates in our population with the worldwide ranges shown in the introduction, it appears that the prescription rate of APs in our sample is rather average, whereas our rates are relatively low for ADs, anxiolytics and hypnotics [9, 10, 13]. When we add our figures to a recent analysis of trends in Dutch PD use, we can conclude that the prevalence of PDs in general, ADs, anxiolytics, and hypnotics is rather similar and constant over time, whereas AP prescription declines [44]. Regarding the correlates, only a few can be compared with previous literature, since most factors have not been studied before. We found that higher emotional distress in nurses due to NPS is related with higher odds of all classes of PD prescription, which is in line with a previous study [13]. Furthermore, just as Azermai et al. [45] we did not find any relations for nurse/residents ratio whereas others did [13, 22]. The absence of a relation with the nurses' profession is fairly in line with the absence found regarding nurses' educational level in the aforementioned study [45]. And although several publications suggest that organizational culture might influence prescription behavior [46-48], our results did not confirm this.

Strengths of this study are that we could extend and deeply explore quantitatively the findings of the qualitative part of the PROPER I study, with a substantial number of residents and nursing home locations throughout the Netherlands. The main limitation is that we had too many variables for confirmatory analyses. On theoretical grounds, there was no reason to exclude any of those, which we tried to overcome by clustering the variables. The concordance between the results of the uni- and multivariate analyses, in which variables were studied independently by correcting for all other variables, adds to the confidence that the clustering did not affect the findings. Also the choice for the levels in the multivariate analyses (e.g. physician instead of DSCU) did not affect the outcome, concluding from the fairly consistent results over the multiple statistical approaches. Finally, since we chose for a cross-sectional instead of a longitudinal design for feasibility reasons, we could not draw conclusions on causal relations.

For interpretation of associations with non-resident-related factors, four subjects require comment. First, it is striking that the two statistically significant associations in the multivariate analyses with non-resident related factors both concern the contact between nursing home professional and resident. Although we have to be cautious not to overrate their relevance con-

sidering the number of associations that we studied, the contribution of interpersonal contact in PD prescription may be an important starting point for further research. Second, the strong correlation between the NPI-Q's emotional distress and severity might on one hand indicate that the nurses' view of severity was colored by personally perceived distress, or by emotional distress just upon scoring severity. This weakness of the NPI-Q, as of its mother version the NPI, is known [33, 49], and may have diluted a potential stronger contribution of either the resident-related NPI severity or the non-resident-related *mindset* factor NPI distress. On the other hand, the correlation between NPI severity and distress may as well implicate that NPS were so far erroneously identified as determinant, meaning that nurses' distress due to NPS might just as well be the main contributor to PD prescription. Third, it may be interesting to differentiate between the theoretical possibilities to operationalize the qualitative themes. Operationalization of the factors within the clusters *mindset* and *communication and cooperation* and part of those within *external possibilities/limitations* into measurable variables is rather complex. A questionnaire may not be able to comprise these psychosocial concepts, social interactions within and between groups of people cannot be reduced to one-on-one relations, and evaluating a number of variables may be insufficient to unravel reality. In contrast, this complexity is less applicable for the quantifiable measures among the *external possibilities/limitations* (physician's availability per resident, number of residents per DSCU, nurse/resident ratios and number of different caregivers). The absence of significant associations of these quantifiable variables is a stronger indication that those are not likely to contribute to PD prescription. Fourth, the wide ranges in prescription rates between different locations and DSCUs, and the large unexplained variance illustrate that the complexity of PD prescribing is yet not unraveled.

Tentatively interpreting these exploratory findings for clinical practice, it is important to be aware of the possibly limited extent to which PD prescription can be affected by non-resident-related factors. Future studies may therefore focus on associations with so far unstudied resident-related factors. Nevertheless, the fact that NPS were found to be the strongest correlates suggests that clinical practice should at least target NPS, after all being the indication for PD prescription.

Conclusion

AP prescription in this study is lower than in previous Dutch studies, but the large differences between locations and units leave room for further improvement. Prescription rates of ADs, anxiolytics, and hypnotics are comparable with rates of previous Dutch studies but are internationally rather low. Although this study has some limitations, we investigated many non-resident-related factors meticulously. The relative absence of significant associations suggests that improvement of PD prescribing could provisionally best be targeted at resident-related factors. The low prescription rates in international perspective and prescription rates of AP declining over time suggest that especially AP prescription is improving, although the large differences in prevalence rates between locations and units leave room for enhancement.

References

1. Schneider, L.S., K. Dagerman, and P.S. Insel, *Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials.* Am J Geriatr Psychiatry, 2006. **14**(3): p. 191-210.
2. Knol, W., et al., *Antipsychotic drug use and risk of pneumonia in elderly people.* J Am Geriatr Soc, 2008. **56**(4): p. 661-6.
3. Langballe, E.M., et al., *Short- and long-term mortality risk associated with the use of antipsychotics among 26,940 dementia outpatients: a population-based study.* Am J Geriatr Psychiatry, 2014. **22**(4): p. 321-31.
4. Ballard, C. and J. Waite, *The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease.* Cochrane Database Syst Rev, 2006(1): p. CD003476.
5. McCleery, J., D.A. Cohen, and A.L. Sharpley, *Pharmacotherapies for sleep disturbances in Alzheimer's disease.* Cochrane Database Syst Rev, 2014(3): p. CD009178.
6. Nelson, J.C. and D.P. Devanand, *A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia.* J Am Geriatr Soc, 2011. **59**(4): p. 577-85.
7. Seitz, D.P., et al., *Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic review.* Int Psychogeriatr, 2013. **25**(2): p. 185-203.
8. Stevenson, D.G., et al., *Antipsychotic and benzodiazepine use among nursing home residents: findings from the 2004 National Nursing Home Survey.* Am J Geriatr Psychiatry, 2010. **18**(12): p. 1078-92.
9. de Mauleon, A., et al., *Associated Factors With Antipsychotic Use in Long-Term Institutional Care in Eight European Countries: Results From the RightTimePlaceCare Study.* J Am Med Dir Assoc, 2014. **15**(11): p. 812-818.
10. Dutcher, S.K., et al., *Effect of medications on physical function and cognition in nursing home residents with dementia.* J Am Geriatr Soc, 2014. **62**(6): p. 1046-55.
11. Vasudev, A., et al., *Trends in psychotropic dispensing among older adults with dementia living in longterm care facilities: 2004-2013.* The American Journal of Geriatric Psychiatry, 2015.
12. Maust, D.T., et al., *Psychotropic use and associated neuropsychiatric symptoms among patients with dementia in the USA.* Int J Geriatr Psychiatry, 2016.
13. Zuidema, S.U., et al., *Psychotropic drug prescription in nursing home patients with dementia: influence of environmental correlates and staff distress on physicians' prescription behavior.* Int Psychogeriatr, 2011. **23**(10): p. 1632-9.
14. Nijk, R.M., S.U. Zuidema, and R.T. Koopmans, *Prevalence and correlates of psychotropic drug use in Dutch nursing-home patients with dementia.* Int Psychogeriatr, 2009. **21**(3): p. 485-93.
15. Gustafsson, M., et al., *Association between behavioral and psychological symptoms and psychotropic drug use among old people with cognitive impairment living in geriatric care settings.* Int Psychogeriatr, 2013. **25**(9): p. 1415-23.

16. Foebel, A.D., et al., *Use of Antipsychotic Drugs Among Residents With Dementia in European Long-Term Care Facilities: Results From the SHELTER Study.* J Am Med Dir Assoc, 2014. **15**(12): p. 911-7.
17. Kleijer, B.C., et al., *Variability between nursing homes in prevalence of antipsychotic use in patients with dementia.* Int Psychogeriatr, 2014. **26**(3): p. 363-71.
18. Nishtala, P.S., et al., *Determinants of antipsychotic medication use among older people living in aged care homes in Australia.* Int J Geriatr Psychiatry, 2010. **25**(5): p. 449-57.
19. Kamble, P., et al., *Use of antipsychotics among elderly nursing home residents with dementia in the US: an analysis of National Survey Data.* Drugs Aging, 2009. **26**(6): p. 483-92.
20. Larrayadieu, A., et al., *Associated factors with antipsychotic use in assisted living facilities: a cross-sectional study of 4367 residents.* Age Ageing, 2011. **40**(3): p. 368-75.
21. Blass, D.M., et al., *Medication use in nursing home residents with advanced dementia.* Int J Geriatr Psychiatry, 2008. **23**(5): p. 490-6.
22. Kim, H. and A.L. Whall, *Factors associated with psychotropic drug usage among nursing home residents with dementia.* Nurs Res, 2006. **55**(4): p. 252-8.
23. Testad, I., et al., *Nursing home structure and association with agitation and use of psychotropic drugs in nursing home residents in three countries: Norway, Austria and England.* Int J Geriatr Psychiatry, 2010. **25**(7): p. 725-31.
24. Cohen-Mansfield, J., et al., *Wisdom from the front lines: clinicians' descriptions of treating agitation in the nursing home, a pilot study.* J Am Med Dir Assoc, 2005. **6**(4): p. 257-64.
25. Wood-Mitchell, A., et al., *Factors influencing the prescribing of medications by old age psychiatrists for behavioural and psychological symptoms of dementia: a qualitative study.* Age Ageing, 2008. **37**(5): p. 547-52.
26. Cornege-Blokland, E., et al., *Reasons to prescribe antipsychotics for the behavioral symptoms of dementia: a survey in Dutch nursing homes among physicians, nurses, and family caregivers.* J Am Med Dir Assoc, 2012. **13**(1): p. 80 e1-6.
27. Smeets, C.H., et al., *Factors Related to Psychotropic Drug Prescription for Neuropsychiatric Symptoms in Nursing Home Residents With Dementia.* J Am Med Dir Assoc, 2014. **15**(11): p. 835-840.
28. Bonner, A.F., et al., *Rationales that Providers and Family Members Cited for the Use of Antipsychotic Medications in Nursing Home Residents with Dementia.* J Am Geriatr Soc, 2015. **63**(2): p. 302-8.
29. van der Spek, K., et al., *PROPER I: frequency and appropriateness of psychotropic drugs use in nursing home patients and its associations: a study protocol.* BMC Psychiatry, 2013. **13**(1): p. 307.
30. Koopmans, R.T., et al., *Dutch elderly care physician: a new generation of nursing home physician specialists.* J Am Geriatr Soc, 2010. **58**(9): p. 1807-9.
31. World Medical Association, *Declaration of Helsinki: ethical principles for medical research involving human subjects.* JAMA, 2013. **310**(20): p. 2191-4.
32. Nordic Council on Medicines, *Guidelines for ATC classification*. 1990, WHO Collaborating Center for Drugs Statistics Methodology: Oslo.

33. Kaufer, D.I., et al., *Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory.* J Neuropsychiatry Clin Neurosci, 2000. **12**(2): p. 233-9.
34. de Jonghe, J.F., et al., *[Neuropsychiatric inventory questionnaire (NPI-Q): A validity study of the Dutch form].* Tijdschr Gerontol Geriatr, 2003. **34**(2): p. 74-7.
35. Smalbrugge, M., et al., *Guideline problem behavior*, in 2008: Utrecht.
36. de Jonghe, J.F. and M.G. Kat, *Factor structure and validity of the Dutch version of the Cohen-Mansfield Agitation Inventory (CMAI-D).* J Am Geriatr Soc, 1996. **44**(7): p. 888-9.
37. Zuidema, S.U., et al., *Agitation in Dutch institutionalized patients with dementia: factor analysis of the Dutch version of the Cohen-Mansfield Agitation Inventory.* Dement Geriatr Cogn Disord, 2007. **23**(1): p. 35-41.
38. Orrung Wallin, A., et al., *Psychometric properties concerning four instruments measuring job satisfaction, strain, and stress of conscience in a residential care context.* Arch Gerontol Geriatr, 2013. **57**(2): p. 162-71.
39. Landeweerd JA, B.N., Nissen JMF., *Arbeidsvoldoening bij verplegenden en verzorgenden. De Maastrichtse arbeidssatisfactieschaal voor de gezondheidszorg [Job satisfaction of nurses and nursing assistants. The Maastricht Work Satisfaction Scale for Healthcare.]*, in *Handboek Verpleegkundige innovatie*. 1996, Bohn Stafleu: Houten.
40. Lintern, T., *Quality in Dementia Care: Evaluating Staff Attitudes and Behaviour. PhD Thesis.* 2001, University of Wales: Bangor.
41. de Jonge, J., J.A. Landeweerd, and F.J.N. Nijhuis, *Constructie en validering van de vragenlijst ten behoeve van het project "Autonomie in het werk": (met nieuwe referentiegegevens)*. 1995: Vakgroep Medische Psychologie, Rijksuniversiteit Limburg.
42. Scott-Cawiezell, J., et al., *Nursing home culture: a critical component in sustained improvement.* J Nurs Care Qual, 2005. **20**(4): p. 341-8.
43. van Beek, A.P. and D.L. Gerritsen, *The relationship between organizational culture of nursing staff and quality of care for residents with dementia: questionnaire surveys and systematic observations in nursing homes.* Int J Nurs Stud, 2010. **47**(10): p. 1274-82.
44. Zuidema, S.U., et al., *Trends in psychofarmacagebruik bij patiënten met dementie.* Tijdschrift voor Ouderengeneeskunde, 2015. **2**.
45. Azermai, M., et al., *Geriatric drug utilisation of psychotropics in Belgian nursing homes.* Hum Psychopharmacol, 2011. **26**(1): p. 12-20.
46. Hughes, C.M., et al., *Does organisational culture influence prescribing in care homes for older people? A new direction for research.* Drugs Aging, 2007. **24**(2): p. 81-93.
47. Tjia, J., J.H. Gurwitz, and B.A. Briesacher, *Challenge of changing nursing home prescribing culture.* Am J Geriatr Pharmacother, 2012. **10**(1): p. 37-46.
48. van der Putten, M.J., et al., *Antipsychotic drug prescription rates among Dutch nursing homes: the influence of patient characteristics and the dementia special care unit.* Aging Ment Health, 2014.
49. Kaufer, D.I., et al., *Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale.* J Am Geriatr Soc, 1998. **46**(2): p. 210-5.

Appendix 1. Resident-related factors of psychotropic drug prescription in univariate and multivariate multilevel logistic regression analyses in 559 nursing home residents with dementia.

	AP prescription OR (95% CI)		**AD prescription** OR (95% CI)		**Anxiolytics prescription** OR (95% CI)		**Hypnotics prescription** OR (95% CI)	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Age of resident	**0.96 (0.94-0.99)**	0.97 (0.94-1.00)	0.97 (0.95-1.00)	–	0.98 (0.94-1.01)	–	0.97 (0.94-1.01)	–
Sex of resident								
Male	**1.59 (1.03-2.46)**	–	0.96 (0.63-1.46)	–	0.98 (0.58-1.67)	–	1.33 (0.77-2.28)	–
Female (ref)								
Length of stay at DSCU	1.01 (1.00-1.01)	**1.01 (1.00-1.02)**	1.00 (0.99-1.01)	–	1.00 (0.99-1.01)	–	0.99 (0.98-1.00)	–
Dementia type								
Alzheimer's dementia	1.31 (0.81-2.12)	–	1.20 (0.77-1.85)	–	0.89 (0.51-1.57)	–	1.10 (0.61-1.95)	–
Vascular dementia	1.30 (0.73-2.34)	–	1.14 (0.66-1.96)	–	1.09 (0.56-2.13)	–	1.08 (0.53-2.21)	–
Mixed Alzheimer's /vascular dementia	1.53 (0.79-2.96)	–	0.88 (0.46-1.68)	–	1.37 (0.66-2.86)	–	0.56 (0.21-1.54)	–
Other dementia (ref)								
NPI-Q S psychosis	**1.21 (1.08-1.35)**	–	**1.19 (1.07-1.33)**	–	1.12 (0.99-1.27)	–	1.05 (0.91-1.21)	–
NPI-Q S agitation	**1.18 (1.09-1.26)**	–	**1.10 (1.02-1.17)**	1.07 (1.00-1.15)	1.07 (0.98-1.16)	–	1.05 (0.96-1.15)	–
NPI-Q S depression	**1.27 (1.05-1.54)**	–	**1.43 (1.20-1.71)**	1.19 (0.90-1.58)	1.14 (0.91-1.42)	–	1.12 (0.88-1.42)	–
NPI-Q S anxiety	**1.22 (1.01-1.48)**	–	**1.24 (1.04-1.48)**	–	**1.61 (1.32-1.97)**	**1.64 (1.16-2.30)**	1.23 (0.98-1.54)	–
NPI-Q S nighttime behavior	**1.25 (1.00-1.56)**	–	1.13 (0.91-1.40)	–	**1.39 (1.09-1.79)**	–	**1.62 (1.25-2.09)**	1.51 (1.00-2.28)
CMAI physical aggression	**1.07 (1.04-1.11)**	**1.05 (1.00-1.09)**	**1.03 (1.00-1.06)**	–	1.03 (1.00-1.07)	–	0.99 (0.94-1.03)	–

CMAI physically nonaggressive behavior	**1.07 (1.04-1.10)**	**1.06 (1.03-1.09)**	1.02 (1.00-1.05)	–	**1.05 (1.02-1.08)**	–	**1.06 (1.03-1.10)**	–
CMAI verbally agitated behavior	**1.04 (1.01-1.08)**	–	**1.04 (1.01-1.08)**	–	1.03 (1.00-1.08)	–	1.00 (0.95-1.04)	–

OR: odds ratio, CI: confidence interval, DSCU: dementia special care unit, NPI-Q S: Neuropsychiatric Inventory Questionnaire Severity clusters/symptoms, CMAI: Cohen-Mansfield Agitation Inventory – long form. Ranges: 0 to 6 for NPI-Q S psychosis, 0 to 9 for NPI-Q S agitation, 0 to 3 for NPI-Q S depression, 0 to 3 for NPI-Q S anxiety, 0 to 3 for NPI-Q S nighttime behavior, 8 to 56 for CMAI physical aggression, 7 to 49 for CMAI physically nonaggressive behavior, and 4 to 28 for CMAI verbally agitated behavior. Blank cells represent variables not entered in the multivariate models, and bold/grey shading indicates statistical significance. The criterion to select variables was $p<0.10$. For a description of precision of the selected variables, 95%-CI are presented. ORs are rounded on 2 decimal places, statistical significance is based upon the crude numbers.

Appendix 2. Non-resident-related factors of psychotropic drug prescription in univariate and multivariate multilevel logistic regression analyses in 559 nursing home residents with dementia.

	AP prescription OR (95% CI)		**AD prescription** OR (95% CI)		**Anxiolytics prescription** OR (95% CI)		**Hypnotics prescription** OR (95% CI)	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Mindset								
NPI-Q E psychosis	**1.16 (1.04-1.29)**	–	1.09 (0.99-1.21)	–	**1.16 (1.04-1.31)**	–	1.00 (0.87-1.16)	–
NPI-Q E agitation	**1.15 (1.08-1.23)**	1.05 (0.96-1.14)	**1.08 (1.02-1.15)**	–	**1.08 (1.01-1.16)**	–	1.01 (0.92-1.09)	–
NPI-Q E depression	**1.31 (1.09-1.56)**	–	**1.42 (1.20-1.67)**	1.19 (0.92-1.55)	1.18 (0.96-1.44)	–	1.01 (0.80-1.28)	–
NPI-Q E anxiety	**1.25 (1.05-1.49)**	–	**1.22 (1.04-1.44)**	–	**1.43 (1.19-1.72)**	0.98 (0.72-1.35)	1.11 (0.89-1.38)	–
NPI-Q E nighttime behavior	**1.34 (1.10-1.64)**	–	1.18 (0.97-1.44)	–	**1.42 (1.15-1.76)**	–	**1.44 (1.14-1.80)**	1.07 (0.74-1.54)
SDCS	0.99 (0.82-1.19)	–	1.06 (0.90-1.24)	–	1.01 (0.83-1.22)	–	1.03 (0.83-1.28)	–
MAS-GZ resident contact	1.24 (0.77-1.99)		1.44 (0.97-2.15)	**1.50 (1.00-2.25)**	0.87 (0.54-1.41)	–	1.00 (0.57-1.77)	–
ADQ (physician)	0.98 (0.91-1.06)	1.01 (0.94-1.08)	0.99 (0.93-1.04)	–	0.99 (0.94-1.05)	–	0.94 (0.88-1.00)	0.98 (0.91-1.06)
ADQ (nurse)	1.00 (0.96-1.04)	0.98 (0.94-1.03)	1.02 (0.98-1.05)	–	1.01 (0.97-1.05)	–	1.02 (0.97-1.07)	–
Knowledge and experience								
Profession (nurse)								
Nursing assistant	0.59 (0.23-1.55)	–	0.89 (0.39-2.00)	–	1.02 (0.38-2.72)	–	0.54 (0.17-1.73)	–
Certified nursing assistant	1.02 (0.61-1.69)	–	1.04 (0.67-1.61)	–	1.16 (0.68-1.97)	–	0.70 (0.40-1.22)	–
Registered nurse (ref)								

Number of years employed at DSCU (nurse)	1.00 (0.96-1.03)	–	1.00 (0.97-1.03)	–	0.99 (0.95-1.04)	–	1.00 (0.96-1.05)	–
Number of years working as physician	1.00 (0.98-1.03)	1.01 (1.00-1.02)	1.00 (0.98-1.02)	–	1.00 (0.98-1.02)	–	1.02 (0.99-1.04)	–
Number of months working at DSCU (physician)	1.01 (1.00-1.02)	–	1.00 (1.00-1.01)	–	1.00 (0.99-1.01)	–	1.00 (0.99-1.01)	–
Communication and cooperation								
MAS-GZ colleague contact	1.12 (0.69-1.81)	–	1.09 (0.72-1.65)	–	0.87 (0.53-1.42)	–	0.94 (0.54-1.66)	–
MAS-GZ clarity	1.30 (0.75-2.28)	1.40 (0.78-2.52)	0.83 (0.53-1.31)	–	0.98 (0.58-1.65)	–	0.77 (0.43-1.41)	–
External possibilities/limitations								
Work Stress Scale	1.02 (0.67-1.56)	–	1.04 (0.73-1.48)	–	1.14 (0.75-1.73)	–	0.77 (0.46-1.27)	–
CVFS Clan culture	0.98 (0.91-1.05)	–	1.01 (0.95-1.06)	–	1.01 (0.95-1.08)	0.90 (0.80-1.00)	1.07 (0.98-1.17)	0.93 (0.83-1.05)
CVFS Adhocracy culture	1.01 (0.92-1.11)	–	1.05 (0.97-1.14)	–	0.95 (0.87-1.04)	0.90 (0.80-1.01)	0.96 (0.87-1.07)	0.91 (0.77-1.08)
CVFS Hierarchy culture	0.99 (0.91-1.08)	–	0.96 (0.89-1.04)	–	1.03 (0.94-1.12)	–	1.00 (0.90-1.10)	0.89 (0.74-1.08)
CVFS Market culture	1.03 (0.96-1.11)	–	0.98 (0.93-1.04)	–	1.00 (0.93-1.08)	–	1.10 (0.99-1.22)	–
Nurse/resident ratio during day * 1000	1.00 (0.99-1.01)	–	1.00 (0.99-1.00)	–	1.00 (0.99-1.01)	–	1.00 (0.99-1.01)	–
Nurse/resident ratio during night * 1000	1.00 (0.99-1.02)	–	1.01 (1.00-1.02)	–	1.00 (0.98-1.01)	–	0.98 (0.97-1.00)	0.98 (0.97-1.00)
Physicians' availability per resident	0.97 (0.94-1.00)	**0.96 (0.93-1.00)**	0.98 (0.96-1.00)	0.98 (0.96-1.00)	1.01 (0.99-1.04)	–	1.00 (0.97-1.03)	–
Number of residents per DSCU	1.01 (0.98-1.05)	–	1.00 (0.98-1.02)	–	0.99 (0.97-1.02)	–	0.99 (0.96-1.02)	–
Number of different caregivers	1.00 (0.97-1.03)	–	0.99 (0.97-1.01)	–	1.00 (0.97-1.02)	–	0.98 (0.95-1.01)	–

OR: odds ratio, CI: confidence interval, NPI-Q E: Neuropsychiatric Inventory Questionnaire Emotional distress clusters/symptoms (range 0 to 10 for psychosis, 0 to 15 for agitation, 0 to 5 for depression, for anxiety, and for nighttime behavior), SDCS: Strain in Dementia Care Scale (range 1 to 16), MAS-GZ: Maastricht Work Satisfaction Scale for Healthcare (range 1 to 5 for each subscale), ADQ: Approaches to Dementia Questionnaire (range 19 to 95), DSCU: dementia special care unit, CVFS: Competing Values Framework Scale (range 0 to 18). The Work Stress Scale ranges from 1 to 5. Blank cells represent variables not entered in the multivariate models, and bold/grey shading indicates statistical significance. The criterion to select variables was $p<0.10$. For a description of precision of the selected variables, 95%-CI are presented. ORs are rounded on 2 decimal places, statistical significance is based upon the crude numbers.

Arts: Er zijn zeker situaties dat het gewoon nodig is, als mensen psychotisch zijn, hallucinaties hebben. [...] En soms [...] ga je toch overstag om psychofarmaca te starten terwijl je het gevoel hebt waren we één op één met deze bewoner dan was het niet nodig geweest.

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Chapter 5

Efficacy of antipsychotics in dementia depended on the definition of patients and outcomes: a meta-epidemiological study

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Claudia H. W. Smeets

Sytse U. Zuidema

Tessa A. Hulshof

Martin Smalbrugge

Debby L. Gerritsen

Raymond T. C. M. Koopmans

Hendrika J. Luijendijk

Abstract

Objective: Postulating that efficacy of antipsychotics for agitation and psychosis in dementia is best estimated in trials among patients with these symptoms and with symptom-specific outcomes, we investigated whether clinically broader definitions affected the pooled efficacy.

Study design and setting: Trials were searched in multiple databases and categorized according to patient population (agitated, psychotic, mixed) and outcome scale (agitation, psychosis, generic). Standardized mean differences with 95% confidence intervals were calculated for conventional and atypical antipsychotics separately.

Results: Thirty trials met our inclusion criteria. Conventional antipsychotics might have a small effect in agitated patients on agitation scales (-0.44; -0.88, 0.01), and in psychotic patients on psychosis scales (-0.31; -0.61, -0.02). There was no effect on generic scales. Efficacy of atypical antipsychotics was not established in agitated patients on agitation scales (-0.15; -0.43, 0.13), and in psychotic patients on psychosis scales (-0.11; -0.20, -0.03), but was small in mixed patients on agitation scales (-0.29; -0.40, -0.18).

Conclusion: Pooled efficacy of antipsychotics for agitation and psychosis in dementia is biased when based on trials that included patients without these target symptoms, or on results measured with generic scales. This finding is important for reviewers and guideline developers who select trials for reviews.

Introduction

Systematic reviews and guidelines are key information sources for clinicians who wish to practice evidence-based medicine. To ensure the validity of review results, reviewers usually adhere to internationally accepted methods, such as those described in the Cochrane Handbook and GRADE recommendations [1, 2]. Both methods advise to define the research question in terms of the Patients, Intervention of interest, Comparison intervention and Outcome (PICO) a-priori [3]. Subsequently, only those trials that meet this PICO should be included in the review.

Whereas the definition of the intervention of interest and the comparison intervention seem straightforward, the patient population and outcome may deserve more attention. The Cochrane Handbook and GRADE recommendations emphasize that they need to be determined meticulously. Patients should be defined 'sufficiently broad' but 'sufficiently narrow' to include the most important characteristics [1]. If efficacy is pooled across different patient populations in which it cannot be expected to be similar, there is a risk that results of a review are not meaningful or even misleading [1, 4]. With respect to defining the outcome, it is advised to focus on outcomes that are likely to be clinically relevant, and to exclude those that are 'trivial or meaningless' [1]. Pooled results based on irrelevant or intermediate outcomes might be deceptive, and may be a reason to rate down the quality of evidence [1, 4].

A problem with defining the patients and outcome appears to exist in reviews about the efficacy of antipsychotics for agitation and psychosis in dementia. Those reviews have included not only trials among patients with agitation or psychosis, but also trials among patients with neuropsychiatric symptoms (NPS) in general [5-8]. NPS can consist of agitation and psychosis, but also of depression, anxiety, night-time behavior or appetite change. As a result, those reviews were based on patients who did not necessarily all have the target symptom agitation or psychosis. For example, they may have included also patients with only depression.

Furthermore, reviews on the efficacy of antipsychotics for agitation and psychosis in dementia have pooled results that were not exclusively based on agitation- and psychosis-specific outcome scales [5-8]. Results based on generic outcome scales such as the Neuropsychiatric Inventory (NPI) and Behavioral Pathology in Alzheimer's Disease Scale (BEHAVE-AD) were included as well [9, 10]. These scales cover not only agitation and psychosis, but also other NPS. Yet, a treatment effect established with a generic scale does not represent the effect on agitation or psychosis specifically, and may reflect a change in any other symptom profile. Such a change could therefore be regarded as less important or indirect to start with.

Current guidelines are based on meta-analyses of trials among patients with any kind of NPS and include treatment effects measured with generic outcome scales. These guidelines support the use of antipsychotic drugs for severe agitation and for psychosis in dementia [11-15]. Usually, they differentiate between conventional and atypical antipsychotics for their pharmacological

properties, presumed mechanisms of effect, and side effect profiles. Some guidelines recommend the atypical antipsychotic risperidone as drug of first choice, or alternatively the conventional antipsychotic haloperidol [11, 13-15].

We postulated that the best estimate for efficacy of antipsychotics in patients with dementia and agitation, respectively psychosis, is assessed in patients with the target symptom (i.e. indication) and measured with a target-specific outcome scale. We investigated whether a broad definition of patients and outcome, differs clinically from a target-specific definition, for the pooled efficacy of antipsychotics for agitation and psychosis in dementia.

The aim of this study was to assess:

1. the efficacy of conventional and atypical antipsychotics measured in patients with dementia and agitation or psychosis, and measured with agitation- or psychosis-specific outcome scales,
2. the efficacy of antipsychotics in patients with dementia and any type of NPS, and measured with agitation- or psychosis-specific outcome scales; and
3. the efficacy of antipsychotics in patients with dementia and agitation or psychosis, measured with generic outcome scales for NPS.

Methods

Search

Two researchers (TAH and HJL) searched Pubmed, Embase, Cinahl, and the Cochrane Library through August 2017 for reported trials. In addition, references of systematic reviews and meta-analyses were hand-searched for relevant trials. For unpublished trials, we searched 17 trial registration websites and the databases of the Dutch Medicines Evaluation Board and the U.S. Food and Drug Administration. Search terms included individual generic drug names in the group N05A of the World Health Organization Anatomical Therapeutic Chemical classification, 'dementia', and 'trial' [16].

We screened title and abstracts of the hits, followed by full text review of potentially eligible studies. We included trials that met the following criteria according to two independent reviewers (CS, HJL): 1) a randomized trial, 2) testing efficacy of oral antipsychotics against placebo, 3) in patients with Alzheimer's, vascular and/or mixed dementia, and 4) who had agitation, psychosis, or NPS in general. We used no restrictions with regard to duration, language or publication date.

Data extraction

A pair of reviewers (TAH, CS, or HJL) independently extracted the following descriptive data per trial: type of the antipsychotic drug, type of dementia, exclusion criteria with regard to psychiatric disorders including substance abuse, number of patients randomized per arm, setting, country, publication year, and trial duration. Based on the eligibility criteria of every trial, we (CS

and HJL) categorized each trial into three types of patient populations: 1) dementia and (at least) agitation, 2) dementia and (at least) psychosis, or 3) dementia and any type of NPS.

We (CS and HJL) extracted the trial results in terms of the reduction in agitation, psychosis and generic NPS in the active treatment and placebo group independently, i.e. the mean change from baseline to end point with standard deviations (SDs) as measured with an agitation-specific (sub)scale, psychosis-specific (sub)scale, and generic scale respectively. For studies that used more than one scale for one outcome, we used the scale that was the reported primary outcome, and otherwise the most frequently used scale across trials. If no specific instrument for agitation or psychosis was used, we extracted the reported relevant subscale of the generic instrument (e.g. NPI-psychosis of the NPI). If only subscales of agitation- or psychosis-specific scales (e.g. the subscale Physically Non-Aggressive Behavior of the Cohen-Mansfield Agitation Inventory (CMAI)) were reported, we did not extract these data for risk of selective reporting. For trials with multiple atypical antipsychotic groups or groups with different doses, we calculated average changes and SDs for the combined groups.

We used the standard error, p-value, t-value or confidence interval (CI) to calculate missing SDs. If this information was missing as well, we imputed the SD with that from another trial or cohort study with the same patient population and outcome scale [17]: we used the SDs of Tariot 2006 to impute the SD in the trials of Barnes 1982, Petrie 1982, and Devanand 1998, and the SDs of Finkel 1995 in the trial of Auchus 1997 [18-23]. Discrepancies in study selection and data extraction were discussed until consensus was reached (CS and HJL).

Statistical analysis

For each combination of patients and outcome, we pooled trial results using standard meta-analysis. Because different scales were used for one outcome, we calculated standardized mean differences (SMDs) with 95% confidence intervals (CIs). Analyses for conventional and atypical antipsychotic trials were performed separately. We applied a fixed effects model when heterogeneity between the trials was low (I-squared below 40% and p-value of standard chi-square statistic above 0.05), and otherwise a random-effects model [24]. All analyses were performed using Stata statistical software version 13.1.17 (StataCorp, College Station, Texas). We applied the traditional SMD cut-offs to compare the pooled results: we interpreted -0.2 or lower as a negligible treatment effect, -0.2 to -0.5 as a small treatment effect (noticeably smaller than medium but not so small as to be trivial), -0.5 to -0.8 as a medium effect (likely to be visible to the naked eye of a careful observer), and above -0.8 as a large effect [25].

Sensitivity analyses

We conducted three sensitivity analyses: (1) including only trials with haloperidol and risperidone, since they are the most frequently studied and used conventional respectively atypical antipsychotic drug; (2) including only trials among patients with agitation but without psychosis; (3) including only trials that did not require imputation of missing data.

Results

Our search strategy yielded 2363 hits, of which 44 underwent full text review [18-23, 26-63]. Thirty trials met the inclusion criteria [18-23, 26-48, 63]. All trials were written in English. Six of these did not provide data that could be pooled, but we describe these results narratively as part of our review [28-31, 34, 63]. Figure 1 presents our search including reasons for exclusion.

Figure 1. Flow diagram of literature search and study selection

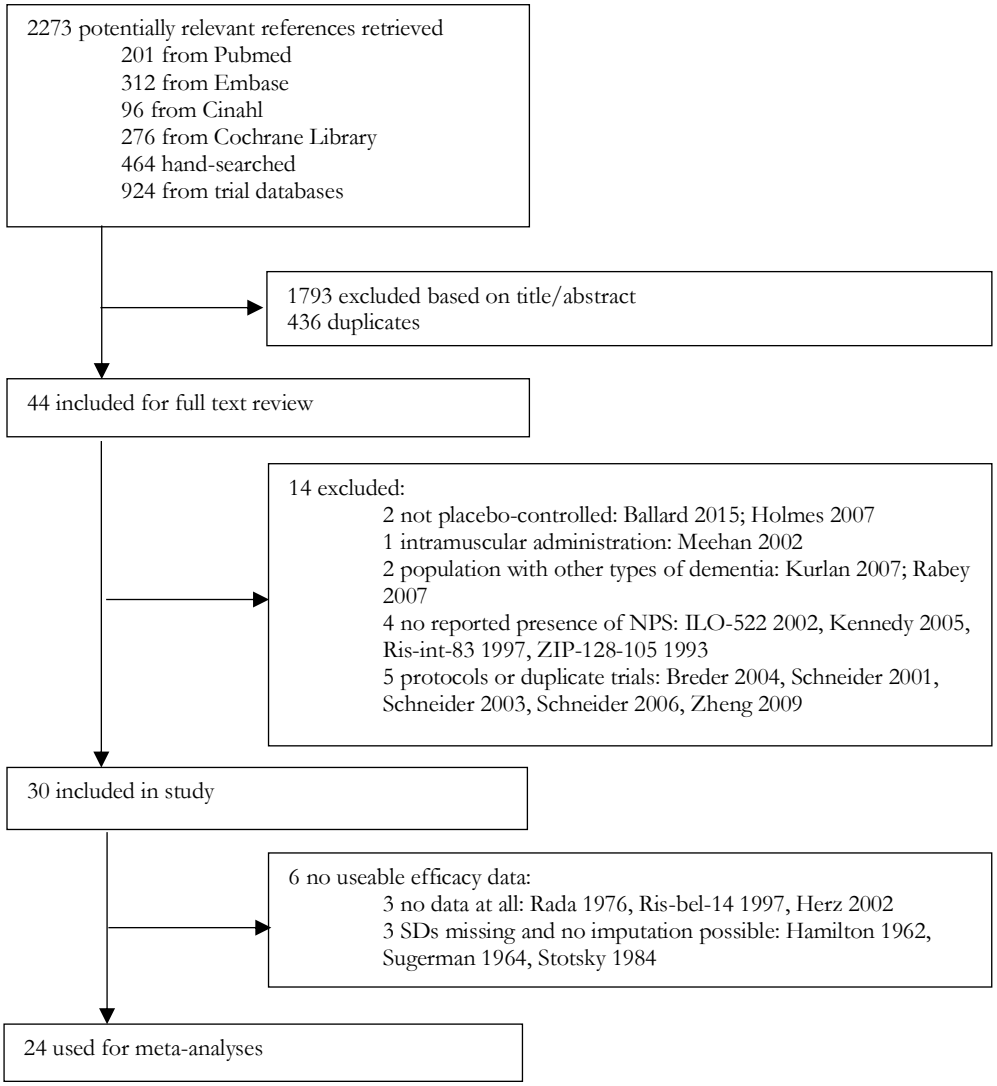


Table 1 summarizes the general study characteristics of the 30 trials. The trial populations consisted of patients with Alzheimer's, vascular, or mixed dementia that resided in nursing homes, hospitals, or the community. The trials included 12 to 652 patients, lasted 2.5 to 36 weeks, and were published between 1962 and 2008. Eleven trials assessed conventional antipsychotics (haloperidol, thioridazine, thiothixene, trifluoperazine, loxapine, perphenazine), 16 atypical antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, tiapride), and three assessed both classes of drugs in a three-armed trial.

In eight trials, the investigated patients had agitation, in nine trials psychosis, and in 13 any NPS. Patients with agitation had been defined as eligible for a trial if they had shown aggression, inappropriate verbal or motor activity, hostility, tension, uncooperativeness, excitement, or poor impulse control. Patients with psychosis had been included in a trial if they had had delusions, hallucinations, conceptual disorganization, suspiciousness, or unusual thought content. The category 'any NPS' encompassed trials that had included patients with any NPS. In 21 trials, eligibility had been determined with an assessment instrument, in the other nine trials with the clinical observation of the target symptom by a health care professional or caregiver. Many trials excluded patients with a history of psychiatric disorders such as schizophrenia and depression. For details, see Appendix A.

Outcomes had been measured with agitation-specific scales in 14 trials, with psychosis-specific scales in 13 trials and with generic scales that measure NPS in 26 trials.

Table 1 presents the trials we included for each combination of patients and outcome scale. The number of trials that could be included in the meta-analyses varied. For example, in the meta-analysis on efficacy of conventional antipsychotics among patients with agitation and measured with agitation-specific outcomes, we included four trials [22, 23, 26, 27]. For conventional antipsychotics, five of six meta-analyses were based on one trial; the analysis in patients with agitation on agitation outcomes included four trials. For atypical antipsychotics, the meta-analyses were based on two to eight trials.

Table 2 summarizes the pooled efficacy of conventional antipsychotics and atypical antipsychotics by patients and outcome scale. Results of the six trials without poolable data are described narratively in the footnote; these generally confirmed the pooled results. The appendices B, C, and D present the forest plots.

Efficacy of conventional antipsychotics

Conventional antipsychotics had a small treatment effect in patients with agitation on agitation scales (SMD -0.44; 95% CI -0.88 to 0.01), and in patients with psychosis on psychosis scales (SMD -0.31; 95% CI -0.61 to -0.02). Both results included the possibility of a negligible and a large effect. In studies among patients with any kind of NPS, the effect was again small when assessed with agitation scales (SMD -0.28; 95% CI -0.54 to -0.02) and psychosis scales (SMD

Table 1. Study characteristics of antipsychotic trials for NPS in dementia

Publication	Drug	Eligibility criterion	Setting	Country	N	Dura-tion, weeks	Outcome		
							Agitation	Psychosis	Generic
Conventional antipsychotics									
Patients with agitation									
Finkel 1995	thiothixene	CMAI	NH	USA	35	11	CMAI	-	-
Auchus 1997	haloperidol	CMAI	OUT	USA	12	6	CMAI	-	-
Allain 2000[a, c]	haloperidol	MOSES	NH/HOS	Europe	204	3	MOSES I/A	-	-
Teri 2000[c]	haloperidol	clinically	OUT	USA	70	16	CMAI	-	BRSD
Patients with psychosis									
Hamilton 1962	trifluoperazine	clinically	HOS	USA	27	8	-	-	MACC[b]
Tariot 2006[a]	haloperidol	BPRS + NPI	NH	USA	193	10	-	NPI-NH P	BPRS
Patients with any NPS									
Sugerman 1964	haloperidol	clinically	HOS	USA	18	6	-	-	PSC[b]
Rada 1976	thiothixene	clinically	HOS	USA	42	4	-	-	NR[b]
Barnes 1982	thioridazine, loxapine	clinically	NH	USA	53	8	-	-	BPRS
Petrie 1982	loxapine	clinically	HOS	USA	61	8	-	-	BPRS
Stotsky 1984	thioridazine	clinically	NH/HOS	USA	358	4	HS A[b]	-	HS[b]
Devanand 1998	haloperidol	(SADS+BPRS)/ BSSD	OUT	USA	66	6	-	-	BPRS
De Deyn 1999[a]	haloperidol	BHV-AD	NH	Europe, Canada	229	12	BHV-AD A	BHV-AD P	BHV-AD
Pollock 2002	perphenazine	NRS	NH	USA	54	2.5	NRS A[b]	NRS P[b]	NRS
Atypical antipsychotics									
Patients with agitation									
Allain 2000[a, c]	tiapride	MOSES	NH/HOS	Europe	205	3	MOSES I/A	-	-
Herz 2002	risperidone, olanzapine	CGS+ADAS/B PRS	UNK	USA	29	6	CMAI[b]	-	BPRS[b]
Brodaty 2003	risperidone	CMAI	NH	Australasia	345	12	CMAI[b]	-	BHV-AD
Ballard 2005	quetiapine	CMAI + NPI	NH	UK	62	6	CMAI	-	-
Zhong 2007	quetiapine	PANSS-EC	NH	USA	333	10	CMAI	-	NPI-NH

Publication	Drug	Eligibility criterion	Setting	Country	N	Dura-tion, weeks	Outcome		
							Agitation	Psychosis	Generic
Patients with psychosis									
Satterlee 1995	olanzapine	BHV-AD	UNK	UNK	238	8	-	-	BHV-AD
De Deyn 2004	olanzapine	clinically	NH/HOS	worldwide	652	10	-	NPI-NH P	NPI-NH
Deberdt 2005	risperidone, olanzapine	NPI-NH	NH/OUT	USA	494	10	-	NPI-NH P	NPI
De Deyn 2005	aripiprazole	NPI	OUT	USA	208	10	-	NPI-NH P	NPI
Mintzer 2006	risperidone	BHV-AD	NH	USA	473	8	-	BHV-AD P	BHV-AD
Tariot 2006[a]	quetiapine	BPRS	NH	USA	190	10	-	NPI-NH P	BPRS
Mintzer 2007	aripiprazole	NPI-NH	NH	worldwide	487	10	-	NPI-NH P	NPI-NH
Streim 2008	aripiprazole	NPI-NH	NH	USA	256	10	-	NPI-NH P	NPI-NH
Patients with any NPS									
Ris-bel-14 1997	risperidone	clinically	UNK	UNK	39	4	-	-	NR[b]
De Deyn 1999[a]	risperidone	BHV-AD	NH	Europe, Canada	229	12	BHV-AD A	BHV-AD P	BHV-AD
Katz 1999	risperidone	BHV-AD	NH	USA	625	12	BHV-AD A	BHV-AD P	BHV-AD
Street 2000	olanzapine	NPI-NH	NH	USA	206	6	NPI-NH A	NPI-NH P	NPI-NH
Sultzer 2008	risperidone, olanzapine, quetiapine	BPRS/NPI	OUT	USA	421	36	BPRS A	BPRS P	BPRS
Paleacu 2008	quetiapine	NPI	UNK	Israel	40	6	NPI A	NPI P	NPI

[a] Trials that investigated both conventional and atypical antipsychotics.
[b] Although measured, no useable data
[c] Patients with psychosis excluded

A: agitation subscore; ADAS: Alzheimer's Disease Assessment Scale [64]; BHV-AD: Behavior Pathology in Alzheimer's Disease Rating Scale [10]; BPRS: Brief Psychiatric Rating Scale [65]; BRSD: Behavioral Rating Scale for Dementia [66]; BSSD: Behavioral Syndromes Scale for Dementia [67]; CGS: abbreviation not written in full [34]; CMAI: Cohen-Mansfield Agitation Inventory [68]; HOS: hospitalized; HS: modified Hamilton Anxiety Scale (no reference reported); I/A: irritability/aggressiveness subscale; MACC: Motility Affect Cooperation Communication behavioral adjustment scale [69]; MOSES: Multidimensional Observation Scale for Elderly Subjects [70]; N: number of patients randomized; NH: nursing home; NPI: Neuropsychiatric Inventory [9]; NPI-NH: Neuropsychiatric Inventory – Nursing Home version [71]; NR: used instrument was not reported; NRS: Neurobehavioral Rating Scale [72]; OUT: outpatient; P: psychosis subscore; PANSS-EC: Positive and Negative Syndrome Scale - Excitement Component [73]; PSC: Psychiatric Symptom Checklist (no reference reported); SADS: Schedule for Affective Disorders and Schizophrenia [74]; UNK: unknown.

-0.23; 95% CI -0.49 to 0.04), and confidence intervals were wide again. Among studies in which the effect was assessed with generic NPS scales, the point estimates did not indicate an effect in patients with agitation (SMD -0.00; 95% CI -0.47 to 0.47) or psychosis (SMD -0.04; 95% CI -0.33 to 0.26).

Efficacy of atypical antipsychotics

Atypical antipsychotics had a negligible effect with a wide confidence interval in patients with agitation measured with agitation outcome scales (SMD -0.15; 95% CI -0.43 to 0.13). The treatment effect in patients with psychosis on psychosis outcome scales was negligible as well (SMD -0.11; 95% CI -0.20 to -0.03). When assessed in patients with any NPS, a small treatment effect on agitation outcomes was found (SMD -0.29; 95% CI -0.40 to -0.18), and a negligible effect on

Table 2. Efficacy of antipsychotic drugs according to patients and outcome

	Outcomes		
	Agitation SMD (95% CI) n/N	**Psychosis** SMD (95% CI) n/N	**Generic** SMD (95% CI) n/N
Conventional antipsychotics			
Patients with agitation	-0.44‡ (-0.88, 0.01) 4/4	NA	-0.00 (-0.47, 0.47) 1/1
Patients with psychosis	NA	-0.31 (-0.61, -0.02) 1/1	-0.04 (-0.33, 0.25) 1/2[a]
Patients with any NPS	-0.28 (-0.54, -0.02) 1/3[b]	-0.23 (-0.49, 0.03) 1/2[c]	NA
Atypical antipsychotics			
Patients with agitation	-0.15§ (-0.43, 0.13) 3/5[d]	NA	-0.22† (-0.55, 0.11) 2/3[e]
Patients with psychosis	NA	-0.11 (-0.20, -0.03) 7/7	-0.10 (-0.19, -0.02) 8/8
Patients with any NPS	-0.29 (-0.40, -0.18) 5/5	-0.13 (-0.24, -0.02) 5/5	NA

‡ random effects analysis; heterogeneity chi² = 7.42, df = 3 (p = 0.060); I² = 59.6%; Tau² = 0.1121
§ random effects analysis; heterogeneity chi² = 4.42, df = 2 (p = 0.110); I² = 54.7%; Tau² = 0.0320
† random effects analysis; heterogeneity chi² = 3.92, df = 1 (p = 0.048); I² = 74.5%; Tau² = 0.0419
n/N: number of trials included in the meta-analysis per number of trials that measured this specific outcome and specific patients, NPS: neuropsychiatric symptoms. a: No data from one negative trial (n = 27) [28]. b: Excluding one positive trial that reported 0.9 improvement in the intervention group versus 0.2 in the placebo group (p < 0.001) on the agitation item of the modified Hamilton Anxiety Scale ranging from 1 to 5 (n = 358) [31]; and one negative trial that reported no significant difference between intervention and placebo (n = 54) [33]. c: Excluding one negative trial that reported no significant difference between intervention and placebo (n =54) [33]. d: Excluding two trials that reported only results of CMAI subscales: one positive trial that reported 7.5 point improvement on the CMAI aggression subscale in the intervention group versus 3.1 point in the placebo group (p < 0.001), and 7.3 point improvement on the CMAI non-aggression subscale in the intervention group versus 2.8 point improvement in the placebo group (p = 0.002) (n = 345) [35]; and one trial that reported non-statistical difference on one CMAI item (n = 29) [34]. e: Excluding one trial that reported only the results on some BPRS items (n = 29) [34].

psychosis outcomes (SMD -0.13; 95% CI -0.24 to -0.02). In patients with agitation, measurements with generic NPS scales yielded a small effect with a wide confidence interval (SMD -0.22; 95% CI -0.55 to 0.11), and a negligible effect (SMD -0.11; 95% CI-0.19 to -0.02) in patients with psychosis.

Sensitivity analyses

The sensitivity analyses for trials with haloperidol and risperidone showed results that were clinically similar to those from all conventional, respectively all atypical antipsychotics (see table 3). One exception was the meta-analysis of risperidone in patients with agitation on agitation outcome scales, for which no data were available. The sensitivity analysis that included trials among patients with agitation and no psychosis, showed clinically similar results for conventional antipsychotics [26, 27]. For atypical antipsychotics however, including the additional trial yielded a small effect on agitation outcomes (SMD -0.39; 95% CI -0.67 to -0.11), in contrast to when this trial was excluded (SMD -0.15; 95% CI -0.43 to 0.13) [26]. The sensitivity analysis excluding trials with imputed data gave similar effect sizes to the analyses including these trials [19-21, 23].

Table 3. Efficacy of haloperidol and risperidone according to patients and outcome

	Outcomes		
	Agitation	**Psychosis**	**Generic**
	SMD (95% CI) n/N	SMD (95% CI) n/N	SMD (95% CI) n/N
Haloperidol			
Patients with agitation	-0.30 [-0.53, -0.06] 3/3	NA	-0.00 [-0.47, 0.47] 1/1
Patients with psychosis	NA	-0.31 [-0.61, -0.02] 1/1	-0.04 [-0.33, 0.26] 1/1
Patients with any NPS	-0.28 [-0.54, -0.02] 1/1	-0.23 [-0.49, 0.04] 1/1	NA
Risperidone			
Patients with agitation	- - 0/2[a]	NA	-0.38 [-0.61, -0.16] 1/2[b]
Patients with psychosis	NA	-0.05‡ [-0.30, 0.20] 2/2	0.06 [-0.10, 0.21] 2/2
Patients with any NPS	-0.27 [-0.40, -0.14] 3/3	-0.18 [-0.31, -0.04] 3/3	NA

‡ random effects analysis; heterogeneity chi^2 =2.55, df = 1 (p = 0.110) I^2 = 60.8%; Tau^2 = 0.0202

n/N: number of trials included in the meta-analysis per number of trials that measured this specific outcome and specific patients, NPS: neuropsychiatric symptoms. a: Excluding two trials that reported only results of CMAI subscales or items: one positive trial that reported 7.5 point improvement on the CMAI aggression subscale in the intervention group versus 3.1 point in the placebo group (p < 0.001), and 7.3 point improvement on the CMAI non-aggression subscale in the intervention group versus 2.8 point improvement in the placebo group (p = 0.002) (n = 345) [35]; and one trial that reported non-statistical difference on one CMAI item (n = 29) [34]. b: Excluding one trial that did not report the results on the BPRS (n = 29) [34].

Discussion

Our meta-epidemiological study shows that the effect of conventional antipsychotics on agitation and psychosis might be underestimated when assessed with generic outcome scales compared to symptom-specific scales. By contrast, efficacy of atypical antipsychotics on agitation is conceivably overestimated when assessed in patients with diverse NPS and with a generic outcome scale. This implies that the precise definition of patients and choice of outcome scales affects the reported pooled efficacy of antipsychotics on agitation and psychosis in dementia. It is important to consider the potential impact of an accurate definition of the target symptom when defining trial selection criteria for a review.

Efficacy of antipsychotics in other reviews

We found that conventional antipsychotics had a small but statistically not significant treatment effect on agitation in patients with dementia and agitation (SMD -0.44; 95% CI -0.88 to 0.01), and a small treatment effect on psychosis in patients with dementia and psychosis (SMD -0.31; 95% CI -0.61 to -0.02). One prior review assessed the effect of conventional antipsychotics, that is haloperidol, on agitation in dementia [6]. This review, that included two trials in patients with any NPS, reported a negligible effect on agitation (SMD -0.12; 95% CI -0.31 to 0.08), but a small effect on aggression (SMD -0.31; 95% CI-0.49 to -0.13) [21, 32]. Including studies in patients with any NPS instead of with agitation specifically, might have diluted the effect of conventional antipsychotics on agitation. We found no published meta-analysis of conventional antipsychotics on psychosis outcomes to compare with our results.

For atypical antipsychotics, our meta-analysis yielded a negligible and statistically nonsignificant effect on agitation (SMD -0.15; 95% CI -0.43 to 0.13), and a negligible significant effect on psychosis (SMD -0.11; 95% CI -0.20 to -0.03). It is difficult to compare these findings with those from prior reviews that differentiated between individual antipsychotics and doses and partly reported weighted mean differences [7, 8]. Nevertheless, those reviews reported modest effects on aggression (with or without agitation) and on psychosis. Around half of the trials included in those reviews had been performed in patients with any kind of NPS. Our results indicate that the reviews' selection of trials among patients with diverse NPS might have led to overestimated efficacy of atypical antipsychotics.

Strengths and limitations

To the best of our knowledge, we are the first to study how the definition of patients and outcomes in reviews has affected the pooled efficacy of antipsychotics in dementia. We investigated conventional and atypical antipsychotics, and also the most widely used antipsychotics haloperidol and risperidone in particular. The main limitation of our study is the uncertainty around some point estimates due to the small number of trials or patients. This was especially the case for the meta-analyses of trials about conventional antipsychotics among patients with target

symptoms and symptom-specific outcome scales. In some trials, outcomes of interest had been measured but not reported, or not reported in full [30, 33-35, 63]. For instance, we chose not to include results measured with subscales or items if results on total scales were not available, because these results may have been biased by selective reporting.

Bias

We postulated that the best estimate for efficacy of antipsychotics for agitation and psychosis in dementia, is obtained from target-specific patients and outcomes. Differences between 'target-specific' and 'non-target-specific' results of meta-analyses, indicate the presence of bias. Such bias can occur as a result of different interpretations on how to define the patients, or the outcome.

Bias due to the imprecise definition of patients

Efficacy of atypical antipsychotics on agitation appears to be higher when assessed among patients with any kind of NPS. There are a number of possible explanations for this finding. First, atypical antipsychotics may reduce other NPS that are related to agitation. Second, the efficacy of individual antipsychotics may differ. For instance, in the meta-analysis of agitation scales in trials among patients with agitation, the tiapride trial showed small efficacy for agitation, whereas the two quetiapine trials showed none (see forest plots in Appendix B.3) [26, 36, 37]. An unequal distribution of individual drugs between meta-analyses may therefore cause bias. Third, there might be an association between publication year and type of patients enrolled in the trials. The three trials in patients with diverse NPS and the highest reported efficacy were published in or before 2000 [26, 32, 45, 46]. An unequal distribution of old and new trials might therefore also cause bias. Fourth, the aim to investigate efficacy on a broad range of NPS, and the reporting of results on items or subscales enholds the risk of positive findings by chance.

Bias due to the imprecise definition of outcome scale

Efficacy might be underestimated for conventional antipsychotics on agitation and psychosis, and overestimated for atypical antipsychotics on agitation when assessed with generic outcome scales. This bias due to definition of the outcome may be caused by an effect of the drugs on neuropsychiatric side effects, such as sedation, if these are included in a generic scale. Sedation, which is linked to increased levels of apathy, might counterbalance a decrease of agitation on generic scales. Bias could also be caused by efficacy on other NPS, such as co-existing agitation in the treatment of psychosis, or treatment of underlying psychosis when reduction of agitation was aimed for. Although generic outcomes may be of added value to symptom-specific outcomes, it is crucial to specifically interpret those that are clinically relevant. Furthermore, trials that assessed but did not report symptom-specific outcomes, need to be included in reviews because the missing outcomes can be considered a potential source of selective reporting.

Implications

Our study implies that trial selection criteria and extracted data should reflect a review's PICO in detail including the target symptom and outcome for the treatment of interest. The Cochrane Handbook and GRADE instructions address that the definition of patients and outcome as part of the research question can be challenging [4]. For the definition of the patients, there is evidently a balance between including sufficiently narrow, but not excluding relevant trials. Nevertheless, Cochrane describes a list of factors to consider for defining the patients, among which 'What are the most important characteristics?' Our results show that for efficacy of antipsychotics on agitation or psychosis in dementia, it is crucial that the target symptoms agitation, respectively psychosis, are considered an important characteristic for the PICO and selection of trials. Our results also demonstrate that it is important to interpret the pooled results on generic outcome scales with caution.

Conclusion

Our study shows that reviewers and guideline developers should define PICOs that represent the symptom of interest, and select trials accordingly. Trials among patients without these specific symptoms may give inaccurate estimates, as will trial results based on non-specific outcome scales. We conclude that the pooled efficacy of conventional and atypical antipsychotics is biased when based on trials that included patients without these target symptoms, and when generic outcome scales are used.

References

1. Higgins, J. and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration.
2. Guyatt, G., et al., *GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables.* J Clin Epidemiol, 2011. **64**(4): p. 383-94.
3. Counsell, C., *Formulating questions and locating primary studies for inclusion in systematic reviews.* Ann Intern Med, 1997. **127**(5): p. 380-7.
4. Guyatt, G.H., et al., *GRADE guidelines: 2. Framing the question and deciding on important outcomes.* J Clin Epidemiol, 2011. **64**(4): p. 395-400.
5. Maglione, M., et al., *Off-Label Use of Atypical Antipsychotics: An Update*. 2011: Rockville (MD).
6. Lonergan, E., et al., *Haloperidol for agitation in dementia.* Cochrane Database Syst Rev, 2010(12).
7. Ballard, C. and J. Waite, *The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease.* Cochrane Database Syst Rev, 2006(1): p. CD003476.
8. Ma, H., et al., *The efficacy and safety of atypical antipsychotics for the treatment of dementia: a meta-analysis of randomized placebo-controlled trials.* J Alzheimers Dis, 2014. **42**(3): p. 915-37.
9. Cummings, J.L., et al., *The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia.* Neurology, 1994. **44**(12): p. 2308-14.
10. Reisberg, B., S.R. Auer, and I.M. Monteiro, *Behavioral pathology in Alzheimer's disease (BEHAVE-AD) rating scale.* Int Psychogeriatr, 1996. **8 Suppl 3**: p. 301-8; discussion 351-4.
11. Nederlandse Vereniging voor Klinische Geriatrie, *Richtlijn Diagnostiek en Behandeling van dementie*. 2014.
12. National Institute for Health and Clinical Excellence, *Dementia: supporting people with dementia and their carers in health and social care.* 'NICE Clinical Guideline 42', 2006.
13. American Psychiatric Association, *The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia.* 2016.
14. Guideline Adaptation Committee, *Clinical Practice Guidelines and Principles of Care for People with Dementia. Sydney.* 2016.
15. Smalbrugge, M., et al., *Guideline problem behavior*, in 2008: Utrecht.
16. Nordic Council on Medicines, *Guidelines for ATC classification*. 1990, WHO Collaborating Center for Drugs Statistics Methodology: Oslo.
17. Furukawa, T.A., et al., *Imputing missing standard deviations in meta-analyses can provide accurate results.* J Clin Epidemiol, 2006. **59**(1): p. 7-10.
18. Tariot, P.N., et al., *Quetiapine treatment of psychosis associated with dementia: a double-blind, randomized, placebo-controlled clinical trial.* Am J Geriatr Psychiatry, 2006(1064-7481 (Print)).

19. Barnes, R., et al., *Efficacy of antipsychotic medications in behaviorally disturbed dementia patients.* Am J Psychiatry, 1982. **139**(9): p. 1170-4.
20. Petrie, W.M., et al., *Loxapine in psychogeriatrics: a placebo- and standard-controlled clinical investigation.* J Clin Psychopharmacol, 1982. **2**(2): p. 122-6.
21. Devanand, D.P., et al., *A randomized, placebo-controlled dose-comparison trial of haloperidol for psychosis and disruptive behaviors in Alzheimer's disease.* Am J Psychiatry, 1998. **155**(11): p. 1512-20.
22. Finkel, S.I., et al., *A randomized, placebo-controlled trial of thiothixene in agitated, demented nursing home patients'.* International Journal of Geriatric Psychiatry, 1995. **10**(2): p. 129-136.
23. Auchus, A.P. and C. Bissey-Black, *Pilot study of haloperidol, fluoxetine, and placebo for agitation in Alzheimer's disease.* J Neuropsychiatry Clin Neurosci, 1997. **9**(4): p. 591-3.
24. Deeks, J., J. Higgins, and D. Altman, *Analysing data and undertaking meta-analyses.*, in *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*, J. Higgins and S. Green, Editors. 2011.
25. Cohen, J., *A power primer.* Psychol Bull, 1992. **112**(1): p. 155-9.
26. Allain, H., et al., *Double blind study of tiapride versus haloperidol and placebo in agitation and aggressiveness in elderly patients with cognitive impairment.* Psychopharmacology (Berl), 2000. **148**(4): p. 361-6.
27. Teri, L., et al., *Treatment of agitation in AD: a randomized, placebo-controlled clinical trial.* Neurology, 2000. **55**(9): p. 1271-8.
28. Hamilton, L.D. and J.L. Bennett, *The use of trifluoperazine in geriatric patients with chronic brain syndrome.* J Am Geriatr Soc, 1962. **10**: p. 140-7.
29. Sugerman, A.A., B.H. Williams, and A.M. Adlerstein, *Haloperidol in the psychiatric disorders of old age.* Am J Psychiatry, 1964. **120**: p. 1190-2.
30. Rada, R.T. and R. Kellner, *Thiothixene in the treatment of geriatric patients with chronic organic brain syndrome.* J Am Geriatr Soc, 1976. **24**(3): p. 105-7.
31. Stotsky, B., *Multicenter study comparing thioridazine with diazepam and placebo in elderly, nonpsychotic patients with emotional and behavioral disorders.* Clin Ther, 1984. **6**(4): p. 546-59.
32. De Deyn, P.P., et al., *A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia.* Neurology, 1999. **53**(5): p. 946-55.
33. Pollock, B.G., et al., *Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients.* Am J Psychiatry, 2002. **159**(3): p. 460-5.
34. Herz, L., et al., *A 6-Week, Double-Blind Comparison of Olanzapine, Risperidone, and Placebo for Behavioral Disturbance in Alzheimer's Disease.* J Clin Psychiatry, 2002. **63:11**.
35. Brodaty, H., et al., *A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia.* J Clin Psychiatry, 2003. **64**(2): p. 134-43.
36. Ballard, C., et al., *Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial.* BMJ, 2005. **330**(7496): p. 874.

37. Zhong, K.X., et al., *Quetiapine to treat agitation in dementia: a randomized, double-blind, placebo-controlled study.* Curr Alzheimer Res, 2007. **4**(1): p. 81-93.
38. Satterlee, W., et al., *A clinical update on olanzapine treatment in schizophrenia and in elderly Alzheimer's disease patients.* Psychopharmacol Bull, 1995. **31**(3): p. 534.
39. De Deyn, P.P., et al., *Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease.* Int J Geriatr Psychiatry, 2004. **19**(2): p. 115-26.
40. Deberdt, W.G., et al., *Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia.* Am J Geriatr Psychiatry, 2005. **13**(8): p. 722-30.
41. De Deyn, P., et al., *Aripiprazole for the treatment of psychosis in patients with Alzheimer's disease: a randomized, placebo-controlled study.* J Clin Psychopharmacol, 2005. **25**(5): p. 463-7.
42. Mintzer, J., et al., *Risperidone in the treatment of psychosis of Alzheimer disease: results from a prospective clinical trial.* Am J Geriatr Psychiatry, 2006. **14**(3): p. 280-91.
43. Mintzer, J.E., et al., *Aripiprazole for the treatment of psychoses in institutionalized patients with Alzheimer dementia: a multicenter, randomized, double-blind, placebo-controlled assessment of three fixed doses.* Am J Geriatr Psychiatry, 2007. **15**(11): p. 918-31.
44. Streim, J.E., et al., *A randomized, double-blind, placebo-controlled study of aripiprazole for the treatment of psychosis in nursing home patients with Alzheimer disease.* Am J Geriatr Psychiatry, 2008. **16**(7): p. 537-50.
45. Katz, I.R., et al., *Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group.* J Clin Psychiatry, 1999. **60**(2): p. 107-15.
46. Street, J.S., et al., *Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group.* Arch Gen Psychiatry, 2000. **57**(10): p. 968-76.
47. Sultzer, D.L., et al., *Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial.* Am J Psychiatry, 2008. **165**(7): p. 844-54.
48. Paleacu, D., et al., *Quetiapine treatment for behavioural and psychological symptoms of dementia in Alzheimer's disease patients: a 6-week, double-blind, placebo-controlled study.* Int J Geriatr Psychiatry, 2008. **23**(4): p. 393-400.
49. Ballard, C., et al., *A double-blind randomized placebo-controlled withdrawal trial comparing memantine and antipsychotics for the long-term treatment of function and neuropsychiatric symptoms in people with Alzheimer's disease (MAIN-AD).* J Am Med Dir Assoc, 2015. **16**(4): p. 316-22.
50. Holmes, C., et al., *Risperidone and rivastigmine and agitated behaviour in severe Alzheimer's disease: a randomised double blind placebo controlled study.* Int J Geriatr Psychiatry, 2007. **22**(4): p. 380-1.

51. Meehan, K.M., et al., *Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia.* Neuropsychopharmacology, 2002. **26**(4): p. 494-504.
52. Kurlan, R., et al., *Quetiapine for agitation or psychosis in patients with dementia and parkinsonism.* Neurology, 2007. **68**(17): p. 1356-63.
53. Rabey, J.M., et al., *Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration.* Mov Disord, 2007. **22**(3): p. 313-8.
54. Kennedy, J., et al., *Olanzapine does not enhance cognition in non-agitated and non-psychotic patients with mild to moderate Alzheimer's dementia.* Int J Geriatr Psychiatry, 2005. **20**(11): p. 1020-7.
55. Breder, C., R. Swanink, and R. Marcus. *Dose ranging study of aripiprazole in patients with Alzheimer's dementia [poster]*. in *157th American Association Meeting*. 2004.
56. Schneider, L.S., et al., *National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer disease trial methodology.* Am J Geriatr Psychiatry, 2001. **9**(4): p. 346-60.
57. Schneider, L.S., et al., *Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer's disease trial.* Schizophr Bull, 2003. **29**(1): p. 57-72.
58. Schneider, L.S., et al., *Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease.* N Engl J Med, 2006. **355**(15): p. 1525-38.
59. Zheng, L., et al., *Metabolic changes associated with second-generation antipsychotic use in Alzheimer's disease patients: the CATIE-AD study.* Am J Psychiatry, 2009. **166**(5): p. 583-90.
60. *ILO-522 [unpublished]*. 2002.
61. *Ris-int-83 [unpublished]*. 1997.
62. *ZIP-128-105 [unpublished]*. 1993.
63. *Ris-bel-14 [unpublished]*. 1997.
64. Rosen, W.G., R.C. Mohs, and K.L. Davis, *A new rating scale for Alzheimer's disease.* The American Journal of Psychiatry, 1984. **141**(11): p. 1356-1364.
65. Overall, J.E. and H.M. Rhoades, *Clinician-rated scales for multidimensional assessment of psychopathology in the elderly.* Psychopharmacol Bull, 1988. **24**(4): p. 587-94.
66. Mack, J.L., M.B. Patterson, and P.N. Tariot, *Behavior Rating Scale for Dementia: development of test scales and presentation of data for 555 individuals with Alzheimer's disease.* J Geriatr Psychiatry Neurol, 1999. **12**(4): p. 211-23.
67. Devanand, D.P., et al., *Behavioral syndromes in Alzheimer's disease.* Int Psychogeriatr, 1992. **4 Suppl 2**: p. 161-84.
68. Cohen-Mansfield, J., M.S. Marx, and A.S. Rosenthal, *A description of agitation in a nursing home.* J Gerontol, 1989. **44**(3): p. M77-84.
69. Ellsworth, *The MACC behavioral adjustment scale, Form II* 1962, Western Psychological Services: Beverly Hills

70. Helmes, E., *Multidimensional Observation Scale for Elderly Subjects (MOSES).* Psychopharmacol Bull, 1988. **24**(4): p. 733-45.
71. Wood, S., et al., *The use of the neuropsychiatric inventory in nursing home residents. Characterization and measurement.* Am J Geriatr Psychiatry, 2000. **8**(1): p. 75-83.
72. Levin HS, H.W., Goethe KE, Sisson RA, Overall JE, Rhoades HM, Eisenberg HM, Kalisky Z, Gary HE., *The neurobehavioural rating scale: assessment of the behavioural sequelae of head injury by the clinician.* J Neurol Neurosurg Psychiatry, 1987. **50**(2): p. 183-93.
73. Lindenmayer, J.P., et al., *An excitement subscale of the Positive and Negative Syndrome Scale.* Schizophr Res, 2004. **68**(2-3): p. 331-7.
74. Endicott, J. and R.L. Spitzer, *A diagnostic interview: the schedule for affective disorders and schizophrenia.* Arch Gen Psychiatry, 1978. **35**(7): p. 837-44.

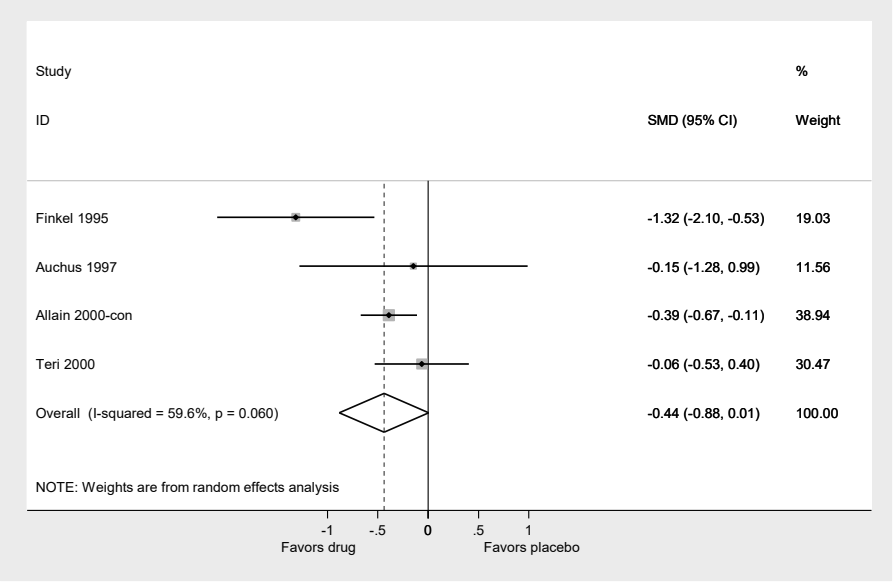
Appendix A. Exclusion criteria

Publication	Exclusion criteria with regard to psychiatric disorders including substance abuse
Conventional antipsychotics	
Patients with agitation	
Finkel 1995	schizophrenia, major depression
Auchus 1997	schizophrenia, schizoaffective disorder, DSM-III-R criteria for major depressive episode or manic episode
Allain 2000	psychiatric disorders such as psychosis, depression
Teri 2000	major psychiatric disorders, delirium, alcohol or drug abuse
Patients with psychosis	
Hamilton 1962	not reported
Tariot 2006	concurrent other Axis I DSM–IV diagnosis
Patients with any NPS	
Sugerman 1964	not reported
Rada 1976	epilepsy, schizophrenia, depressive pseudodementia, pseudosenility
Barnes 1982	schizophrenia
Petrie 1982	schizophrenia
Stotsky 1984	psychosis
Devanand 1998	drug or alcohol dependence
De Deyn 1999	psychiatric disorders
Pollock 2002	delirium, schizophrenia, bipolar disorder, major depressive disorder
Atypical antipsychotics	
Patients with agitation	
Allain 2000	psychiatric disorders such as psychosis, depression
Herz 2002	not reported
Brodaty 2003	major depression, psychiatric disorders that could have accounted for psychotic disturbances
Ballard 2005	not reported
Zhong 2007	schizophrenia, schizoaffective disorder, bipolar disorder, agitation not related to dementia
Patients with psychosis	
Satterlee 1995	not reported
De Deyn 2004	primary mood disorder, other Axis I disorder e.g. schizophrenia, bipolar disorder, delusional disorder
Deberdt 2005	not reported
De Deyn 2005	Axis I DSM–IV diagnosis of delirium, amnesic disorders, bipolar disorder, schizophrenia, schizoaffective disorder; mood disorder with psychotic features; psychotic symptoms due to general medical condition or physiologic substance effects
Mintzer 2006	psychiatric disorders that produce psychotic symptoms; epilepsy
Tariot 2006	Axis I DSM–IV diagnosis
Mintzer 2007	Axis I diagnosis of delirium, amnestic disorder, bipolar disorder, schizophrenia, schizoaffective disorder, mood disorder with psychotic features; major depressive episode with psychotic symptoms; seizure disorders, suicidal ideation or history
Streim 2008	Axis I diagnosis of delirium or schizophrenia; a schizoaffective, mood, bipolar, or amnestic disorder; continuous symptoms of psychosis before onset of dementia; major depression with symptoms of psychosis; at risk of suicide; substance use disorder according to DSM–IV criteria
Patients with any NPS	
Ris-bel-14 1997	psychiatric diagnosis
De Deyn 1999	psychiatric disorders
Katz 1999	delirium or amnestic disorder, psychiatric diagnosis causing psychotic disturbances
Street 2000	Axis I DSM-IV disorder (e.g. schizophrenia, bipolar disorder, depression), non-dementia related psychosis
Sultzer 2008	schizophrenia, schizoaffective disorder, delusional disorder, mood disorder with psychotic features, delirium, in need of psychiatric admission, suicidal
Paleacu 2008	alcohol or drug abuse

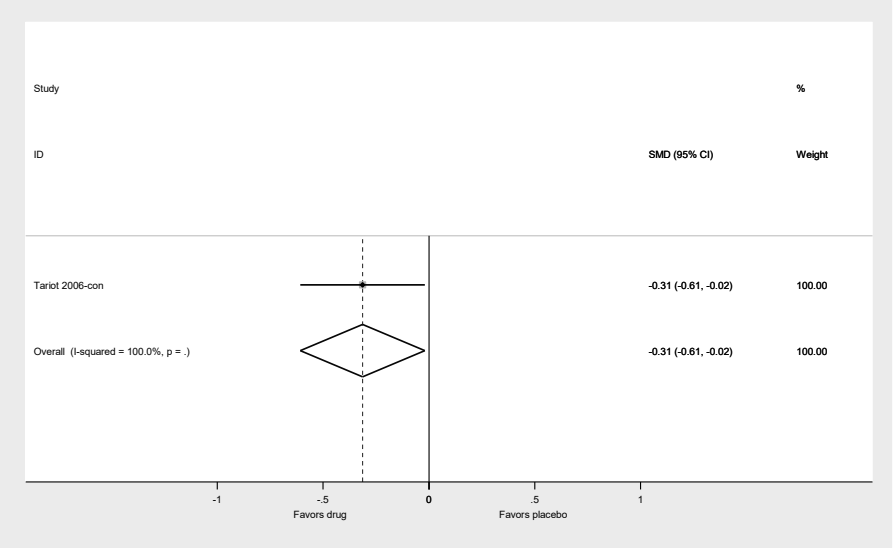
DSM: Diagnostic and Statistical Manual of Mental Disorder

Appendix B. Efficacy of conventional and atypical antipsychotics in patients with agitation on agitation outcomes, and in patients with psychosis on psychosis outcomes.

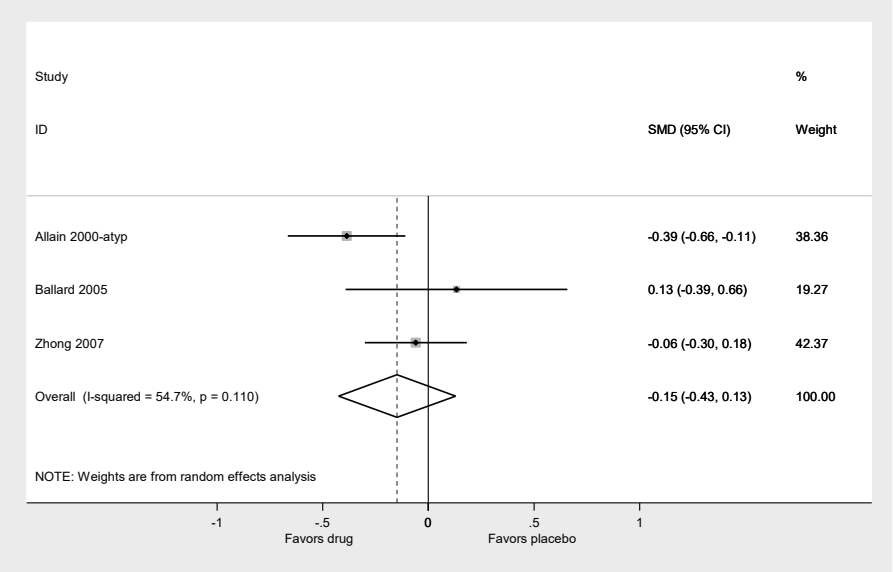
1. Conventional antipsychotics in patients with agitation on agitation outcomes



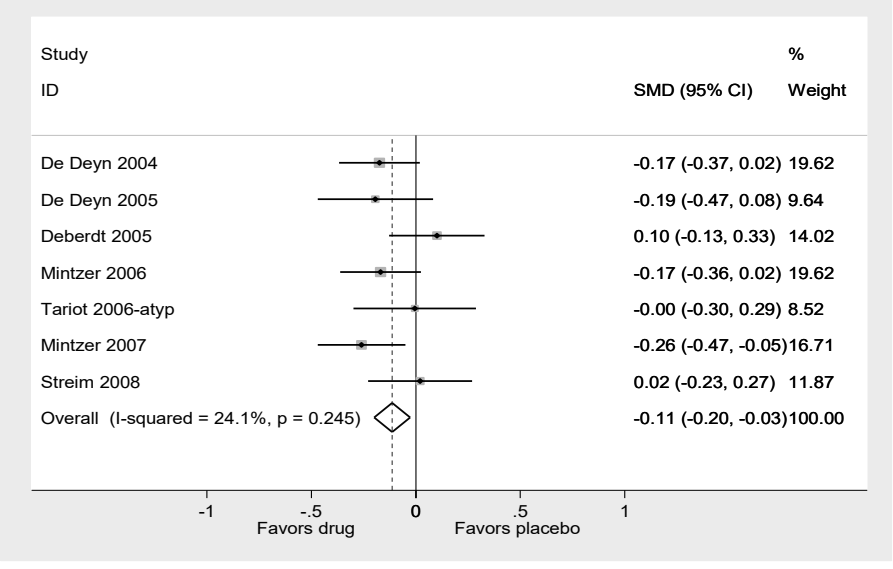
2. Conventional antipsychotics in patients with psychosis on psychosis outcomes



3. Atypical antipsychotics in patients with agitation on agitation outcomes

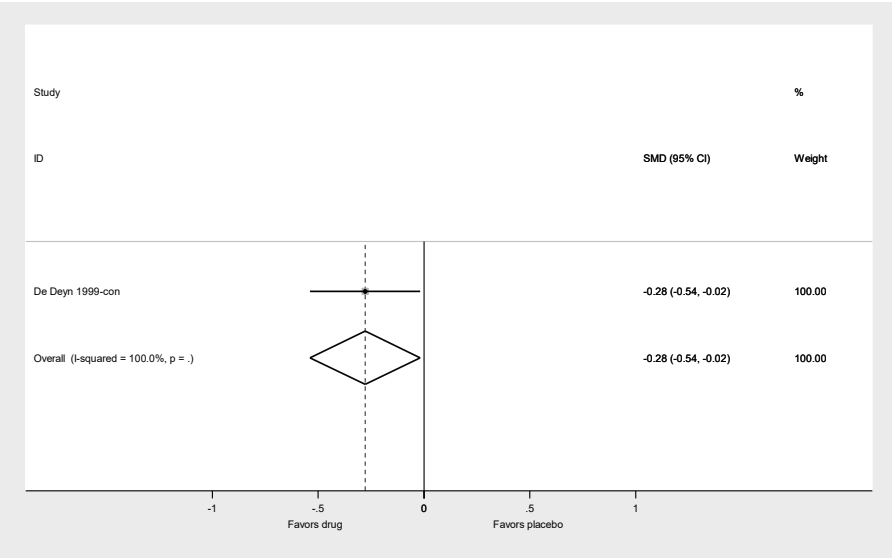


4. Atypical antipsychotics in patients with psychosis on psychosis outcomes

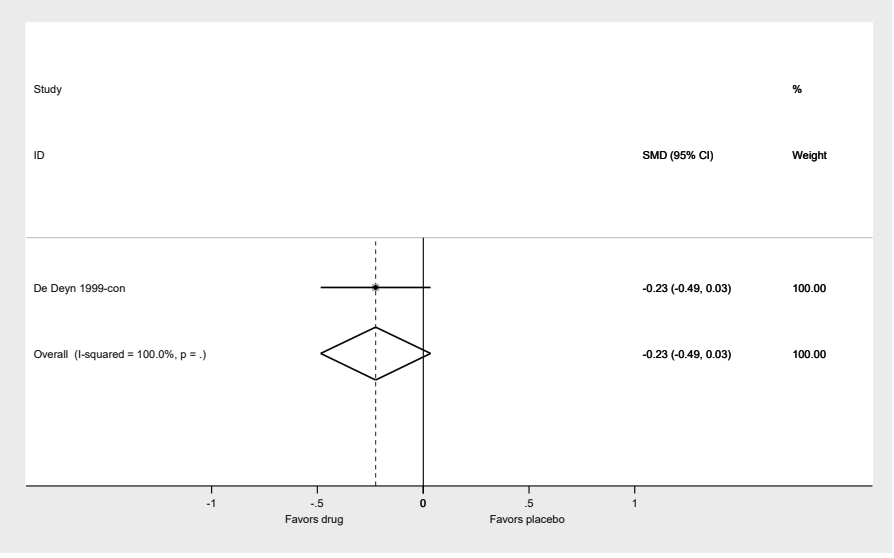


Appendix C. Efficacy of conventional antipsychotics when assessed within patients with any type of NPS, and with generic outcomes.

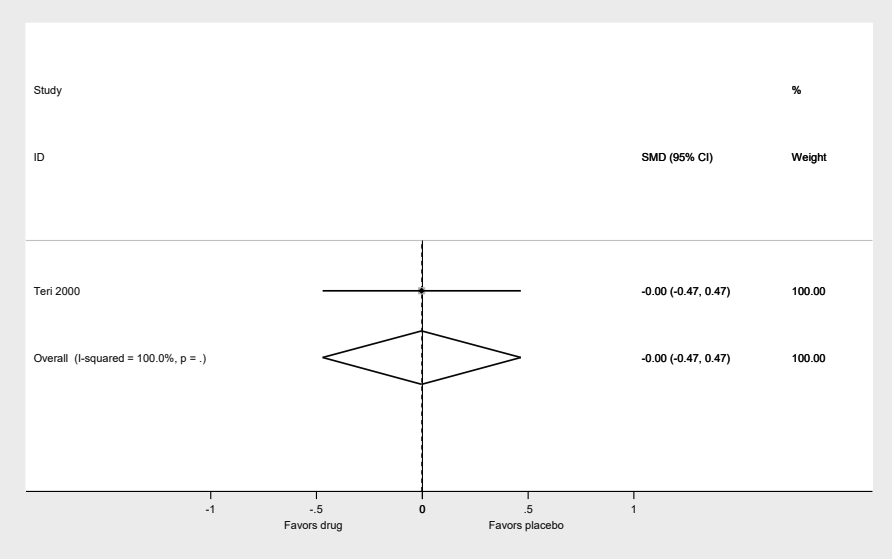
1. Conventional antipsychotics in patients with any type of NPS on agitation outcomes



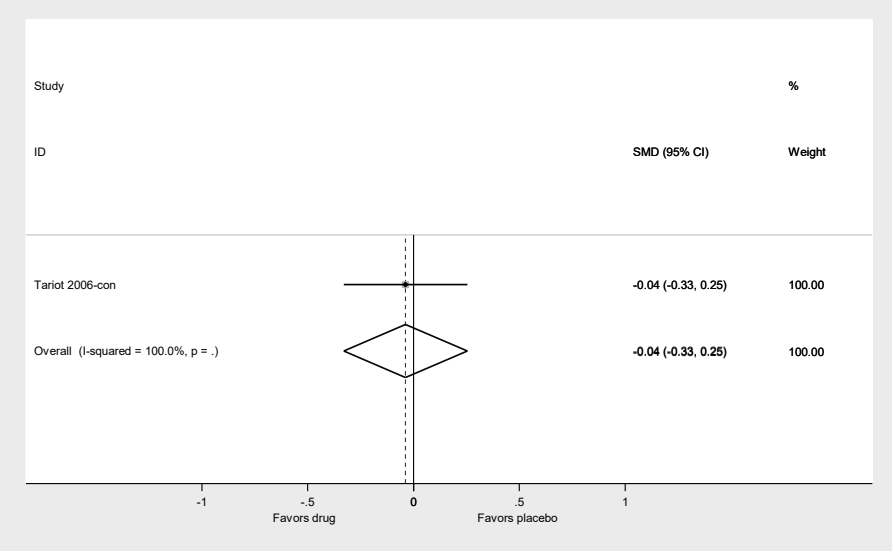
2. Conventional antipsychotics in patients with any type of NPS on psychosis outcomes



3. Conventional antipsychotics in patients with agitation on generic outcomes

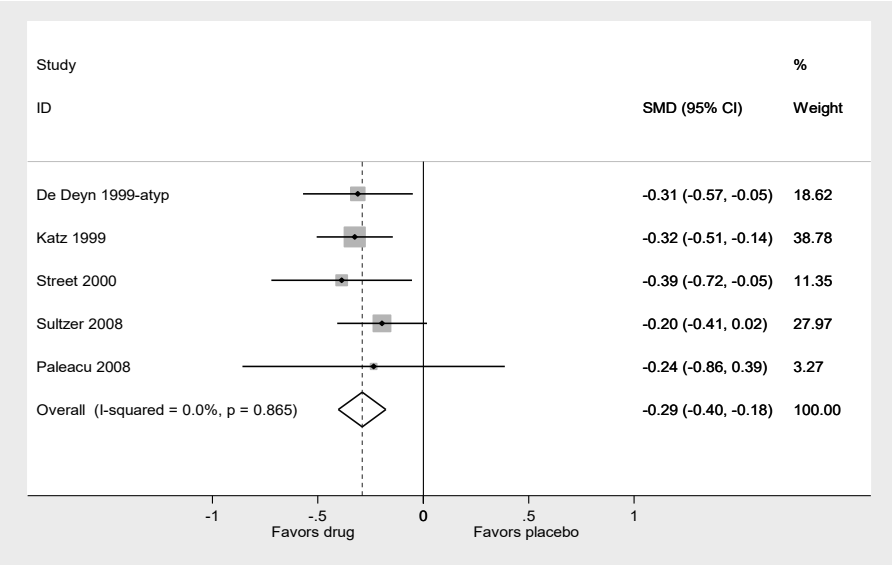


4. Conventional antipsychotics in patients with psychosis on generic outcomes

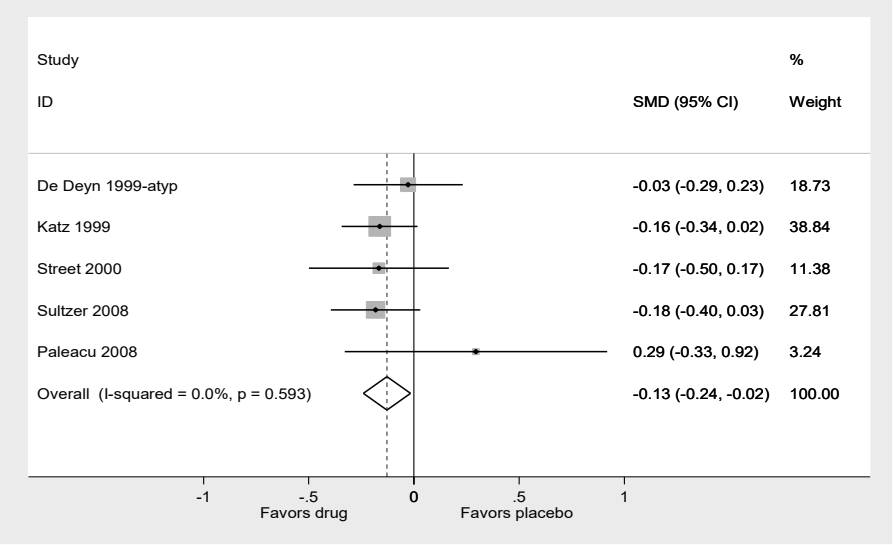


Appendix D. Efficacy of atypical antipsychotics when assessed within patients with any type of NPS, and with generic outcomes.

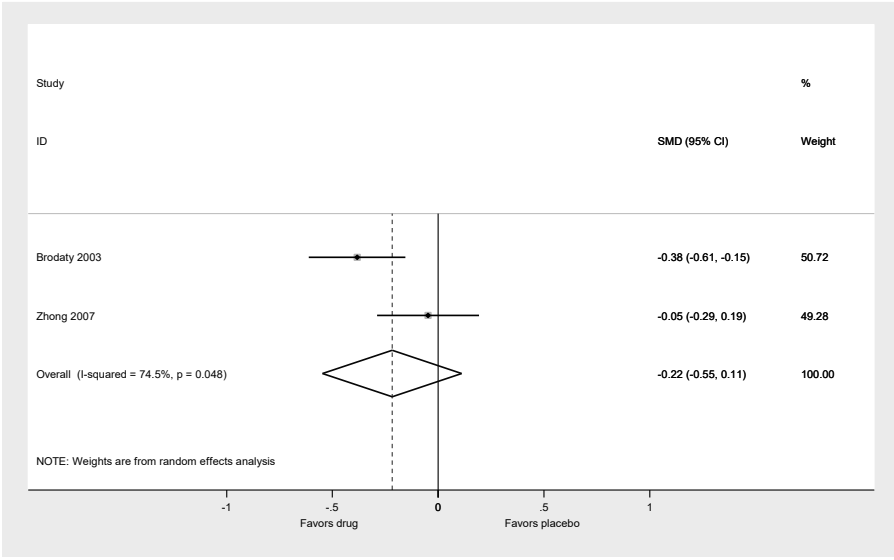
1. Atypical antipsychotics in patients with any type of NPS on agitation outcomes



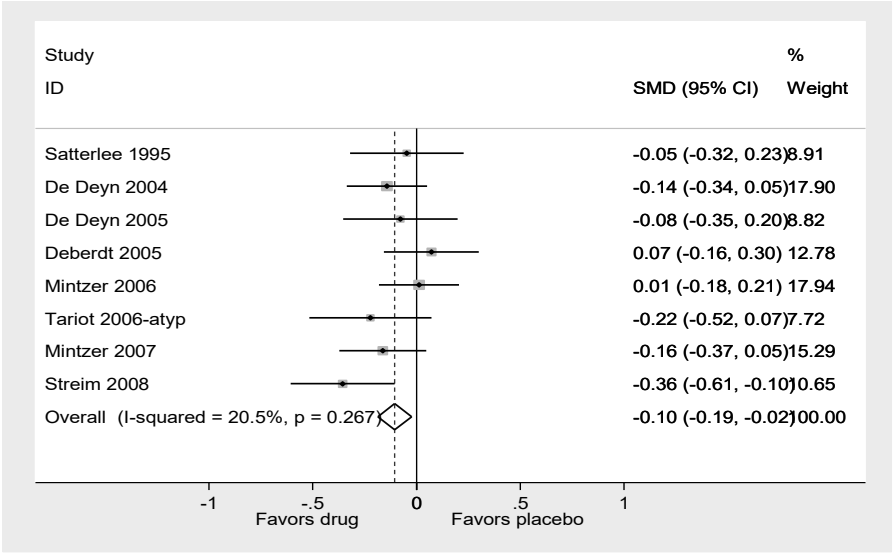
2. Atypical antipsychotics in patients with any type of NPS on psychosis outcomes



3. Atypical antipsychotics in patients with agitation on generic outcomes



4. Atypical antipsychotics in patients with psychosis on generic outcomes



Arts: De familie moet uiteindelijk verder als de patiënt overleden is. En je moet wel het idee hebben dat ze er met een goed gevoel op terug kunnen kijken, de periode tot het overlijden. [...] Dus het kan best zijn dat je dan inderdaad de medicatie gewoon laat staan.

(13199:13687) - D13: S0031

Chapter 6

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

BMC Psychiatry, 2013. 13(1): p. 280

Claudia H.W. Smeets

Martin Smalbrugge

Debby L. Gerritsen

Marjorie H.J.M.G. Nelissen-Vrancken

Roland B. Wetzels

Klaas van der Spek

Sytse U. Zuidema

Raymond T.C.M. Koopmans

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: 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.

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 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 [20], 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 [21], 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.

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) [22], and the Multidisciplinary guideline Polypharmacy in the elderly [23] including the STRIP method and Dutch versions of the START and STOPP tools [24]. The STRIP is the Systematic Tool to Reduce

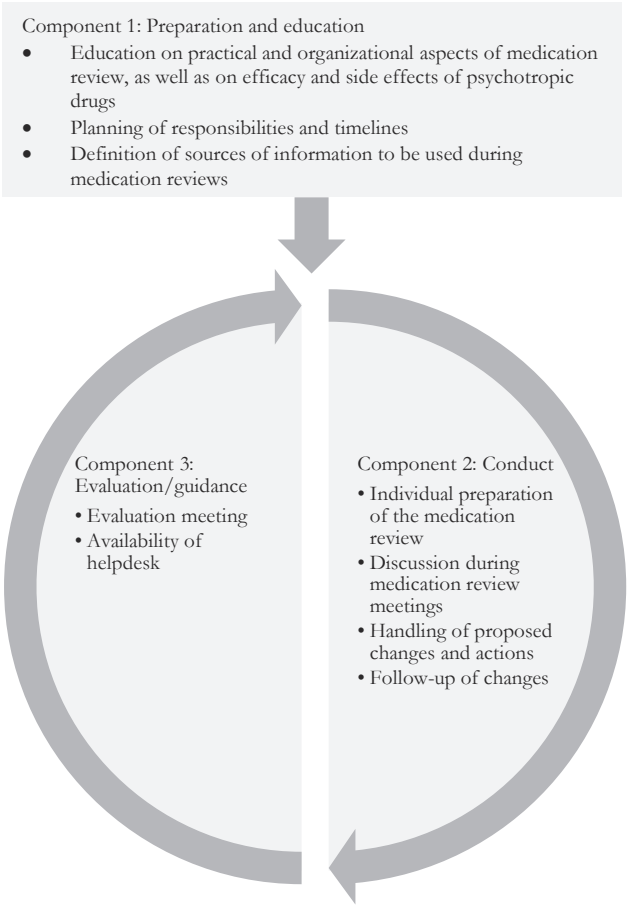


Figure 1. Intervention consisting of three components.

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 [23]. 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.

Assessments

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 [25], 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) [22], the Guideline for diagnostics and medical treatment of dementia of the Dutch Geriatrics Society [26], the drug database of the Royal Dutch Pharmacists Association [27], and the 'Farmacotherapeutisch Kompas' [28], 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 [29] 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 [30] is a brief version of the Neuropsychiatric Inventory, which was developed for measuring NPS in dementia [31]. 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 [32]. 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 [33]. The (construct) validity of the Dutch version [34, 35] and reliability [36] 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 [37]. 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) [38, 39]. 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 [40].

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 [41, 42]. 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 [43]. Additionally, the Revised Index of Social Engagement (RISE) [44] 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 [45], and is derived from the MDS-RAI [38, 46].

Activities of daily living will be assessed using a questionnaire also derived from the MDS-RAI [47], of which validity and reliability of the Dutch version were established [40]. 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) [48]. Cognition will be assessed using the Severe Impairment Battery-8 [49], a brief version of the Severe Impairment Battery [50]. 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.

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 [51], and adapted for the PROPER II study.

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*
Hospitalizations	Number, indication, and duration	Physician
Mortality	Occurrence	Researcher

* or representative
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.

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 [52], a sample size of 21 clusters is sufficient to detect a statistically significant difference applying Russ Lenth software [53] and calculation methods according to Twisk [54]. 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 [55].

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.

References

1. Zuidema, S., R. Koopmans, and F. Verhey, *Prevalence and predictors of neuropsychiatric symptoms in cognitively impaired nursing home patients.* J Geriatr Psychiatry Neurol, 2007. **20**(1): p. 41-9.
2. Seitz, D., N. Purandare, and D. Conn, *Prevalence of psychiatric disorders among older adults in long-term care homes: a systematic review.* Int Psychogeriatr, 2010. **22**(7): p. 1025-39.
3. Wetzels, R.B., et al., *Course of neuropsychiatric symptoms in residents with dementia in nursing homes over 2-year period.* Am J Geriatr Psychiatry, 2010. **18**(12): p. 1054-65.
4. Ballard, C.G., et al., *Management of agitation and aggression associated with Alzheimer disease.* Nat Rev Neurol, 2009. **5**(5): p. 245-55.
5. van Iersel, M.B., et al., *Antipsychotics for behavioural and psychological problems in elderly people with dementia: a systematic review of adverse events.* Drugs Aging, 2005. **22**(10): p. 845-58.
6. Schneider, L.S., K. Dagerman, and P.S. Insel, *Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials.* Am J Geriatr Psychiatry, 2006. **14**(3): p. 191-210.
7. Knol, W., et al., *Antipsychotic drug use and risk of pneumonia in elderly people.* J Am Geriatr Soc, 2008. **56**(4): p. 661-6.
8. Eggermont, L.H., K. de Vries, and E.J. Scherder, *Psychotropic medication use and cognition in institutionalized older adults with mild to moderate dementia.* Int Psychogeriatr, 2009. **21**(2): p. 286-94.
9. Wetzels, R.B., et al., *Prescribing pattern of psychotropic drugs in nursing home residents with dementia.* Int Psychogeriatr, 2011. **23**(8): p. 1249-59.
10. Nijk, R.M., S.U. Zuidema, and R.T. Koopmans, *Prevalence and correlates of psychotropic drug use in Dutch nursing-home patients with dementia.* Int Psychogeriatr, 2009. **21**(3): p. 485-93.
11. Ballard, C., et al., *Management of agitation and aggression associated with Alzheimer's disease: controversies and possible solutions.* Curr Opin Psychiatry, 2009. **22**(6): p. 532-40.
12. van Dijk, K.N., et al., *Drug utilisation in Dutch nursing homes.* Eur J Clin Pharmacol, 2000. **55**(10): p. 765-71.
13. Kaur, S., et al., *Interventions that can reduce inappropriate prescribing in the elderly: a systematic review.* Drugs Aging, 2009. **26**(12): p. 1013-28.
14. Verrue, C.L., et al., *Pharmacists' interventions for optimization of medication use in nursing homes : a systematic review.* Drugs Aging, 2009. **26**(1): p. 37-49.
15. Forsetlund, L., et al., *Effect of interventions to reduce potentially inappropriate use of drugs in nursing homes: a systematic review of randomised controlled trials.* BMC Geriatr, 2011. **11**: p. 16.
16. Stuijt, C.C., et al., *Appropriateness of prescribing among elderly patients in a Dutch residential home: observational study of outcomes after a pharmacist-led medication review.* Drugs Aging, 2008. **25**(11): p. 947-54.

17. Patterson, S.M., et al., *An evaluation of an adapted U.S. model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in northern ireland (fleetwood northern ireland study).* J Am Geriatr Soc, 2010. **58**(1): p. 44-53.
18. Child, A., et al., *A pharmacy led program to review anti-psychotic prescribing for people with dementia.* BMC Psychiatry, 2012. **12**: p. 155.
19. Schols, J.M., H.F. Crebolder, and C. van Weel, *Nursing home and nursing home physician: the Dutch experience.* J Am Med Dir Assoc, 2004. **5**(3): p. 207-12.
20. van der Spek, K., et al., *PROPER I: frequency and appropriateness of psychotropic drugs use in nursing home patients and its associations: a study protocol.* BMC Psychiatry, 2013. **13**(1): p. 307.
21. Instituut voor Verantwoord Medicijngebruik. [cited 2018 10 Dec]; Available from: http://www.medicijngebruik.nl/.
22. Smalbrugge, M., et al., *Guideline problem behavior*, in 2008: Utrecht.
23. *Nederlands Huisartsen Genootschap - Multidisciplinaire richtlijn Polyfarmacie bij ouderen*. 2012; Available from: https://www.nhg.org/themas/artikelen/mdr-polyfarmacie-bij-ouderen.
24. Gallagher, P., et al., *STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation.* Int J Clin Pharmacol Ther 2008. **46**(2): p. 72-83.
25. Hanlon, J.T., et al., *A method for assessing drug therapy appropriateness.* J Clin Epidemiol, 1992. **45**(10): p. 1045-51.
26. Van Gool, W.A., Hagemeijer, A., Barkhof, F., Brouwer, K.J., Eefsting, J.A., Eikelenboom, P., Jonker, C., Olde Rikkert, M.G.M., Sanders, J.B., Scheltens, Ph., Schmand, B.A., Sival, R.C., Stam, C.J., Steenhoek, A., Verhey, F.R.J., Wind, A.W., *Richtlijn Diagnostiek en medicamenteuze behandeling van dementie*, ed. K.v.d.G. CBO. 2005.
27. *KNMP Kennisbank*. Available from: http://www.kennisbank.knmp.nl/index.asp.
28. *Farmacotherapeutisch Kompas*. Available from: http://www.fk.cvz.nl/.
29. Nordic Council on Medicines, *Guidelines for ATC classification*. 1990, WHO Collaborating Center for Drugs Statistics Methodology: Oslo.
30. Kaufer, D.I., et al., *Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory.* J Neuropsychiatry Clin Neurosci, 2000. **12**(2): p. 233-9.
31. Cummings, J.L., et al., *The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia.* Neurology, 1994. **44**(12): p. 2308-14.
32. de Jonghe, J.F., et al., *[Neuropsychiatric inventory questionnaire (NPI-Q): A validity study of the Dutch form].* Tijdschr Gerontol Geriatr, 2003. **34**(2): p. 74-7.
33. Cohen-Mansfield, J., M.S. Marx, and A.S. Rosenthal, *A description of agitation in a nursing home.* J Gerontol, 1989. **44**(3): p. M77-84.
34. de Jonghe, J.F. and M.G. Kat, *Factor structure and validity of the Dutch version of the Cohen-Mansfield Agitation Inventory (CMAI-D).* J Am Geriatr Soc, 1996. **44**(7): p. 888-9.

35. Zuidema, S.U., et al., *Agitation in Dutch institutionalized patients with dementia: factor analysis of the Dutch version of the Cohen-Mansfield Agitation Inventory.* Dement Geriatr Cogn Disord, 2007. **23**(1): p. 35-41.
36. Zuidema, S.U., et al., *Assessing neuropsychiatric symptoms in nursing home patients with dementia: reliability and Reliable Change Index of the Neuropsychiatric Inventory and the Cohen-Mansfield Agitation Inventory.* Int J Geriatr Psychiatry, 2011. **26**(2): p. 127-34.
37. Leontjevas, R., et al., *Nijmegen Observer-Rated Depression scale for detection of depression in nursing home residents.* Int J Geriatr Psychiatry, 2011.
38. Morris, J.N., et al., *Designing the national resident assessment instrument for nursing homes.* Gerontologist, 1990. **30**(3): p. 293-307.
39. Burrows, A.B., et al., *Development of a minimum data set-based depression rating scale for use in nursing homes.* Age Ageing, 2000. **29**(2): p. 165-72.
40. Gerritsen, D., et al., *[Three new observational scales for use in Dutch nursing homes: scales from the Resident Assessment Instrument for Activities of Daily Living, cognition and depression].* Tijdschr Gerontol Geriatr, 2004. **35**(2): p. 55-64.
41. Ettema, T.P., et al., *QUALIDEM: development and evaluation of a dementia specific quality of life instrument--validation.* Int J Geriatr Psychiatry, 2007. **22**(5): p. 424-30.
42. Ettema, T.P., et al., *QUALIDEM: development and evaluation of a dementia specific quality of life instrument. Scalability, reliability and internal structure.* Int J Geriatr Psychiatry, 2007. **22**(6): p. 549-56.
43. Reisberg, B., et al., *The Global Deterioration Scale for assessment of primary degenerative dementia.* Am J Psychiatry, 1982. **139**(9): p. 1136-9.
44. Gerritsen, D.L., et al., *A revised Index for Social Engagement for long-term care.* J Gerontol Nurs, 2008. **34**(4): p. 40-8.
45. Mor, V., et al., *The structure of social engagement among nursing home residents.* J Gerontol B Psychol Sci Soc Sci, 1995. **50**(1): p. P1-P8.
46. Hirdes, J.P., et al., *Integrated health information systems based on the RAI/MDS series of instruments.* Healthc Manage Forum, 1999. **12**(4): p. 30-40.
47. Morris, J.N., B.E. Fries, and S.A. Morris, *Scaling ADLs within the MDS.* J Gerontol A Biol Sci Med Sci, 1999. **54**(11): p. M546-53.
48. Lingjaerde, O., et al., *The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients.* Acta Psychiatr Scand Suppl, 1987. **334**: p. 1-100.
49. Schmitt, F.A., et al., *A brief instrument to assess treatment response in the patient with advanced Alzheimer disease.* Alzheimer Dis Assoc Disord, 2009. **23**(4): p. 377-83.
50. Saxton, J., McGonigle-Gibson, K.L., Swihart, A.A., Miller, V.J. and Boller, F, *Assessment of the severely demented patient: Description and validation of a new neuropsychological test battery.* Psychological Assessment: A Journal of Consulting and Clinical Psychology, 1990. **2**: p. 298-303.

51. van Oostrom, S.H., et al., *[Multimorbidity and comorbidity in the Dutch population--data from general practices]*. Ned Tijdschr Geneeskd, 2011. **155**: p. A3193.
52. Zuidema, S.U., et al., *Psychotropic drug prescription in nursing home patients with dementia: influence of environmental correlates and staff distress on physicians' prescription behavior*. Int Psychogeriatr, 2011. **23**(10): p. 1632-9.
53. *Java applets for power and sample size*. Available from: http://homepage.stat.uiowa.edu/~rlenth/Power/.
54. Twisk, J.W.R., *Applied Multilevel Analysis*. Practical guides to biostatistics and epidemiology. 2006, USA: Cambridge University Press.
55. *WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects*. Available from: http://www.wma.net/en/30publications/10policies/b3/index.html.

Arts: Wanneer iemand dolgelukkig hier dement zit te zijn met haldol of dat soort zaken, dan denk je minder snel van 'weet je wat, zullen we het eens stoppen'?

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Chapter 7

The PROPER intervention: an effective tool for reducing psychotropic drug prescription in nursing home patients with dementia?

Submitted

Claudia H.W. Smeets

Martin Smalbrugge

Raymond T.C.M. Koopmans

Marjorie H.J.M.G. Nelissen-Vrancken

Klaas van der Spek

Steven Teerenstra

Debby L. Gerritsen

Sytse U. Zuidema

Abstract

Objectives: To evaluate the effect of the PROPER intervention in nursing home patients with dementia on the prevalence of psychotropic drug use and neuropsychiatric symptoms.

Design: A cluster-randomized controlled design with two parallel groups (intervention versus usual care) and assessments at 0, 6, 12 and 18 months.

Setting: 31 dementia special care units within 13 long-term care organizations in the Netherlands.

Participants: 380 patients with dementia.

Intervention: The PROPER intervention consisted of a structured and repeated multidisciplinary medication review, supported by education and continuous evaluation.

Measurements: Prescriptions of antipsychotics, antidepressants, anxiolytics, and hypnotics, and occurrence of neuropsychiatric symptoms.

Results: The prescription of any type of psychotropic drugs increased in the intervention group, and decreased in the control group, with an estimated difference of 3.9% per six months ($p=0.01$). Effects for the individual drug groups were minor (differences of 1.6% and below per six months) and not statistically significant. The occurrence of neuropsychiatric symptoms remained stable in both the intervention and control groups during the follow-up of 18 months.

Conclusions: The PROPER intervention failed to demonstrate effectiveness in reducing the prevalence of psychotropic drugs. It may be interesting to enrich the intervention with components that address personal attitudes and communication between nursing home professionals, not only with respect to the prescription of psychotropic drugs, but also to neuropsychiatric symptoms.

Introduction

Neuropsychiatric symptoms are highly prevalent in patients with dementia, especially among those who live in long-term care organizations [1]. These symptoms are frequently treated with psychotropic drugs, despite limited efficacy and enlarged risks of side effects, particularly for antipsychotics [2]. Since the late eighties, trials have been conducted to improve the prescription of psychotropic drugs for nursing home residents. These trials varied in focus (e.g. medication review, involvement of pharmacists and/or nurses, education), geographical location and results [3-9].

In the Netherlands, nursing home care for patients with dementia is organized differently than in most countries. Patients reside at dementia special care units (DSCUs), and medical care is usually provided by physicians who have been educated as elderly care physicians and are employed by the nursing home [10]. When prescribing psychotropic drugs, these physicians can make use of the Guideline for problem behavior of the Dutch body representing Elderly Care Physicians (Verenso) [11].

In order to improve the prescription of psychotropic drugs, we developed the PROPER intervention. This intervention has several key elements. First, it consists of a medication review with a structured and repeated design. Second, it uses a multidisciplinary approach. Aside from the elderly care physician and a pharmacist, a nurse (assistant) is also present. Nurses are expected to add insights on the patients' neuropsychiatric symptoms and side effects, in addition to the medical and pharmacological knowledge. Third, the intervention is largely based on the above-mentioned Guideline for problem behavior, and the Multidisciplinary guideline Polypharmacy in the Elderly [11, 12].

This manuscript reports on secondary outcomes of the PROPER II trial. The primary outcome, the Appropriate Psychotropic Drug use In Dementia index, showed that the PROPER intervention improved the appropriateness of prescription for those psychotropic drugs that were prescribed [13]. The current study is conducted at the patient level. It aims to evaluate the effect of the PROPER intervention in nursing home patients with dementia on 1) the prevalence of psychotropic drug use prescribed for neuropsychiatric symptoms (e.g. antipsychotics, antidepressants, hypnotics, and anxiolytics) and on 2) the occurrence of neuropsychiatric symptoms.

Methods

Design and setting

This study was part of the PROPER II trial, as described in detail elsewhere [14]. We used a cluster-randomized controlled design with two parallel groups (intervention versus usual care) and assessments at 0, 6, 12 and 18 months.

Patients

All patients living in the participating DSCUs were eligible for inclusion if they had a chart diagnosis of dementia. Patients who dropped out were replaced by patients who were newly admitted to the participating DSCUs.

Intervention

We developed a method for a structured and repeated multidisciplinary medication review supported by education and continuous evaluation. The method consisted of three components: 1) preparation and education, followed by a cycle of 2) conduct and 3) evaluation/guidance.

The first component included preparation of organizational aspects, such as assignment of a coordinator, division of tasks, and planning. It also included education of physicians, pharmacists and nurses on how to conduct medication reviews, and on benefits and harms of psychotropic drugs. The education was provided by the Dutch Institute for Rational Use of Medicine [15]. It prescribes adherence to the Guideline for problem behavior of the Dutch Association of Elderly Care Physicians (Verenso), and the Multidisciplinary guideline Polypharmacy in the Elderly (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)) [11, 12, 16].

The second component comprised the actual conduct and follow-up of the medication review by the (elderly care) physician, pharmacist, and a nurse (assistant). Prior to the medication review, each of the participants had to prepare within his or her field of expertise, i.e. to respectively obtain medical information, pharmacological information, and knowledge on the patient's current behavior and presence of potential side effects. During a medication review meeting, the participants discussed the start, continuation, discontinuation, or dose change of psychotropic and other drugs, as well as additional diagnostics and alternative interventions for the management of neuropsychiatric symptoms. Potential changes and actions were registered and proposed to the patient's representative, and followed up by the physician and nurse.

The third component consisted of evaluation meetings on the process of the medication reviews. Positive experiences and benefits, as well as points for improvement were shared during these meetings. They were attended by the participants of the medication reviews, and guided by the IVM. If participants had questions in between the meetings, the IVM was available by means of an online helpdesk.

Assessments

The prescription of psychotropic drugs was assessed as the prescription of one or more drugs from the Anatomical Therapeutic Chemical group of antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), hypnotics (N05C), and any of these four groups [17]. Psychotropic drugs had to be prescribed for neuropsychiatric symptoms explained by the presence of

dementia, for a sleep disorder, or for a delirium. Also, psychotropic drugs for which no indication could be found, were registered. Pro re nata prescriptions were excluded.

Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory-Questionnaire (NPI-Q) and the Cohen-Mansfield Agitation Inventory (CMAI) [18, 19]. The NPI-Q consists of 12 neuropsychiatric symptom items and gives a total severity score ranging from 0 to 36 (with a higher score indicating higher severity), and a total distress score ranging from 0 to 60 (with a higher score indicating higher caregiver distress). We also analyzed the scores for the clusters 'psychosis' and 'agitation', and for the symptoms 'nighttime symptoms', 'anxiety', 'apathy' and 'depressive symptoms' [20]. The CMAI includes 29 items on physical aggression, physically non-aggressive behavior, and verbal agitation, and ranges from 29 to 203 (with a higher score indicating more frequent agitation).

We collected the following baseline characteristics: age, sex, chart type of dementia, and length of stay at the DSCU. We also assessed the stage of dementia using the Global Deterioration Scale (GDS) ranging from 1 to 7 (with a higher stage reflecting more severe dementia) [21].

Data on the prescription of psychotropic drugs, age, sex, type of dementia and length of stay were collected from medical files and medication lists by researchers. Data on neuropsychiatric symptoms were completed via web-based questionnaires by nurses who were directly involved in the patients' care. The web-based GDS questionnaires were completed by the patients' physicians. Patients were not directly involved in the study. Assessments were conducted at baseline, and after 6, 12 and 18 months.

Randomization

Randomization to either the intervention group, or to the care-as-usual group, was conducted at organizational level to avoid contamination of the intervention to the control group. Allocation was computer-generated and conducted by a statistician.

DSCU and patient selection

In line with the sample size calculation of the primary outcome, we included the twelve organizations that had participated in the previously conducted PROPER I study, supplemented with an additional organization to account for potential drop-out of an organization [14]. From each organization, we randomly selected two DSCUs, and from each DSCU 15 patients. If a DSCU had less than 15 patients, we included one or more additional DSCUs in order to reach at least 30 patients per organization.

Statistical analysis

First, data on psychotropic drugs and neuropsychiatric symptoms were aggregated on DSCU level in order to analyze psychotropic drug prevalence rates and mean NPS. Subsequently, we used linear mixed models to account for repeated measurements within DSCUs, which were again nested within organizations. Organization and DSCU were considered random effects, and

time (continuous) and treatment and their interaction as fixed effects. The model assumed equal baseline values, because of the randomization. We assessed model fit by checking the residuals of the mixed models and the observed-versus-predicted-value plots. All analyses were conducted with IBM SPSS Statistics for Windows, Version 22.0. Grouponk, NY: IBM Corp.

Sensitivity analyses

In the process evaluation of this trial, we have seen that one intervention organization did not fully adhere to the intervention procedures: the pharmacist was absent for the education, for some of the medication review meetings and for all evaluation meetings; and the coordinator could not conduct all organizational tasks (Gerritsen, submitted). Also, three control organizations had already conducted medication reviews with a nurse throughout the trial. We conducted two sensitivity analyses to gain further insight into these process evaluation findings.

Ethics

The local Medical Ethics Review Committee 'CMO Regio Arnhem-Nijmegen' rated the study (number 2012/226) and stated that it was in accordance with the applicable Dutch rules concerning review of research ethics committees and informed consent. We followed the principles of the Declaration of Helsinki [22]. The representatives of the patients on the participating DSCUs were informed about the study in writing and given the explicit opportunity to refrain from the patient's participation. The study has been registered in The Netherlands Trial Register (NTR3569).

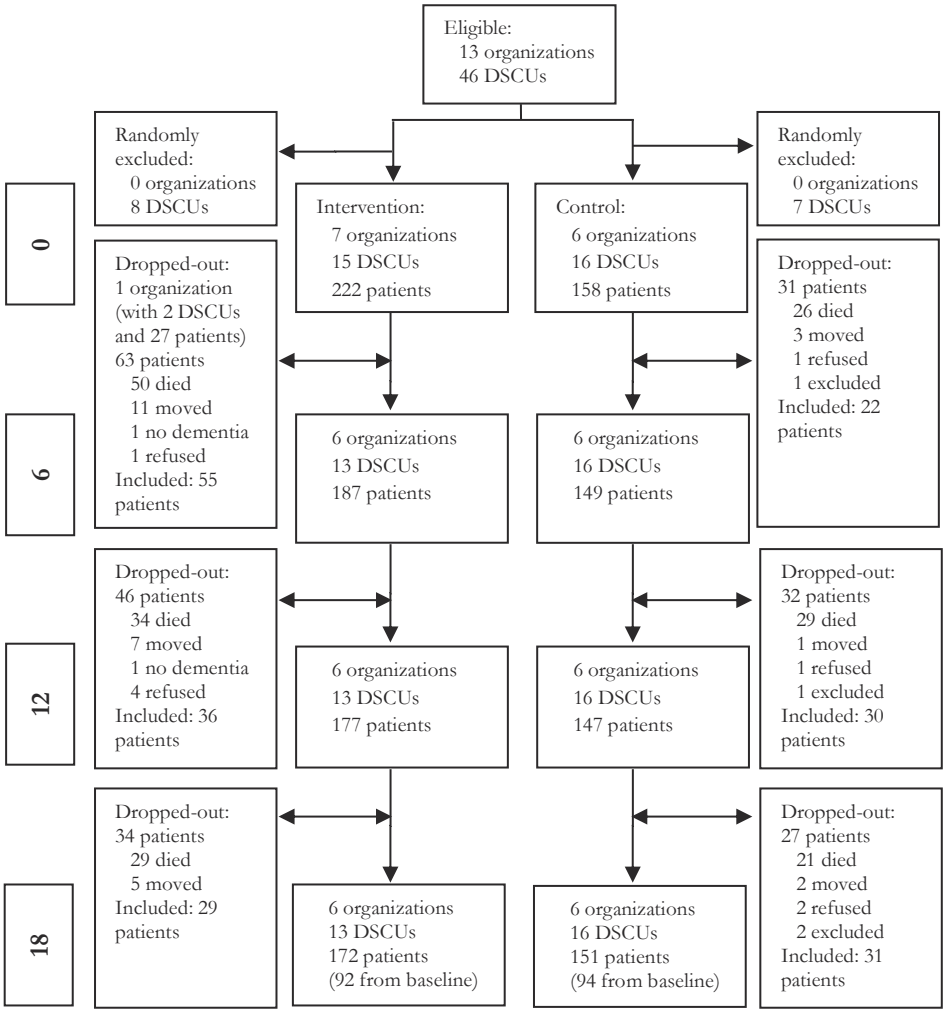
Results

The study was conducted from September 2012 to July 2014. We included thirteen long-term care organizations, which were located throughout the Netherlands. Seven organizations were randomly assigned to the intervention group, and six to continue care as usual. One organization in the intervention group withdrew after the baseline assessment due to departure of the coordinating physician. In the intervention group, the mean number of participants per DSCU was 12, 11, 14, and 13 at baseline, 6, 12 and 18 months respectively, overall range 6 to 20. In the control group, this number was 16 patients (at all assessments), overall range 4 to 19.

Patient flow

A total of 380 patients were included. In the intervention group, 170 patients dropped out (143 due to death, transfer to another unit, or withdrawal during the study and 27 due to the withdrawal of the organization) and were replaced by 120 new patients, versus 90 drop-outs and 83 replacements in the control group. A total of 323 patients completed the final assessment, 186 of whom participated from baseline onwards (92 in intervention and 94 in the control group). Details are shown in figure 1.

Figure 1. Flowchart



Baseline characteristics

Table 1 presents the baseline characteristics. In the intervention group, the proportion of patients with Alzheimer's dementia was higher, versus a higher proportion of vascular and other dementia in the control group. The intervention population had slightly more severe dementia, having the GDS mode at stage 6, versus at stage 5 in the control group. There were no other baseline imbalances.

Table 1. Baseline characteristics

Characteristic	Intervention	Control
Number of patients	222	158
Age in years [SD] (range)	84 [7.4] (55-99)	83 [7.3] (55-99)
Sex N (%)		
Female	173 (78%)	114 (72%)
Male	49 (22%)	44 (28%)
Type of dementia, N (%)		
Alzheimer's dementia	90 (41%)	37 (23%)
Vascular dementia	27 (12%)	29 (18%)
Mixed Alzheimer's/vascular dementia	22 (10%)	19 (12%)
Other dementia	83 (37%)	73 (46%)
GDS N (%)		
Stage 2	0 (0%)	1 (1%)
Stage 3	4 (2%)	5 (3%)
Stage 4	15 (7%)	19 (12%)
Stage 5	47 (21%)	53 (34%)
Stage 6	74 (33%)	41 (26%)
Stage 7	48 (22%)	27 (17%)
Unknown	34 (15%)	12 (8%)
Length of stay at DSCU in months [SD] (range)	25 [21.8] (0-118)	24 [21.7] (0-114)
Psychotropic drug prescription, N (%)		
Any*	107 (48%)	81 (51%)
Antipsychotics	56 (25%)	33 (21%)
Antidepressants	56 (25%)	40 (25%)
Hypnotics	31 (14%)	18 (11%)
Anxiolytics	32 (14%)	27 (17%)
NPI-Q severity [SD] (range)	6.0 [5.1] (0.0-23.0)	6.3 [5.6] (0.0-26.0)
NPI-Q distress [SD] (range)	4.5 [5.5] (0.0-26.0)	5.3 [7.1] (0.0-34.0)
CMAI [SD] (range)	43 [13] (29-87)	45 [16] (29-105)

* Any: any antipsychotic, antidepressant, hypnotic, and/or anxiolytic

Abbreviations: SD: standard deviation; GDS: Global Deterioration Scale; DSCU: dementia special care unit; NPI-Q Neuropsychiatric Inventory – Questionnaire; CMAI: Cohen-Mansfield Agitation Inventory

Theoretical ranges of instruments: NPI-Q severity: 0 – 36; NPI-Q distress: 0 – 60; CMAI: 29 – 203.

Effect

Table 2 shows the observed DSCU means for the different variables, which are also described below. A mixed model with linear trend for the intervention and control groups showed a good fit to the data. Therefore, the effect of the intervention was estimated as the difference in slopes per six months with 95% confidence intervals.

Psychotropic drug prescription

The prevalence of any psychotropic drug prescription increased by 5% (SD 22%) from baseline to the final assessment in the intervention group, and decreased by 8% (SD 13%) in the control group. The estimated difference between the slopes for use of any psychotropic drug increased by 3.9% every six months (p=0.01). Prescription of antipsychotics in the intervention group decreased by 5% (SD 20%) from baseline to 12 months, but then increased again by 4% (SD 6%). In the control group, the antipsychotic prescription consistently decreased by a total of 5% (SD 11%) from baseline to 18 months. Antidepressant nor hypnotic prescriptions did not change in the intervention group, and decreased in the control group by 2% (SD 15%) and 3% (SD 10%) respectively. The prescription of anxiolytics increased by 4% (SD 12%) in the intervention group, and decreased by 1% (SD 9%) in the control group. Slope differences of the individual drug groups were small (1.6% and below) and not statistically significant.

Neuropsychiatric symptoms

Neuropsychiatric symptoms assessed by the NPI-Q remained rather constant and did not show statistically significant slope differences. Also, in the NPI cluster and symptom scores (psychosis, agitation, nighttime symptoms, anxiety, apathy and depressive symptoms), differences were not statistically significant (results not shown in table). Agitation assessed with the CMAI increased slightly by 2.6 points (SD 15.5) in the intervention group and by 0.5 points (SD 10.0) in the control group, leading to a small slope difference of 0.6 every six months, which was not statistically significant.

Sensitivity analyses

Table 3 shows the results of the sensitivity analyses. If we excluded the organization that did not fully adhere to the intervention procedures from the analyses, results were similar. If we excluded the control organizations that conducted medication reviews with a nurse as usual care, the decline in the prescription of any psychotropic drugs and subsequently the slope difference was even greater and remained statistically significant.

Table 2. Results on psychotropic drug prescription and neuropsychiatric symptoms

Variable		Observed DSCU means [SD]				Difference in slopes per 6 months [95% CI]	p
		Baseline	6 months	12 months	18 months		
Any psychotropic drug*	intervention	50% [20%]	54% [19%]	54% [15%]	55% [13%]	3.9% [0.9% - 6.9%]	0.01
	control	50% [17%]	49% [21%]	44% [22%]	42% [16%]		
Antipsychotics	intervention	27% [22%]	24% [17%]	22% [16%]	26% [15%]	1.3% [-1.3% - 4.0%]	0.33
	control	20% [14%]	19% [15%]	18% [18%]	15% [11%]		
Antidepressants	intervention	27% [18%]	29% [20%]	29% [16%]	27% [8%]	0.2% [-2.7% - 3.1%]	0.90
	control	24% [13%]	25% [17%]	26% [17%]	22% [16%]		
Hypnotics	intervention	14% [13%]	17% [11%]	14% [12%]	14% [13%]	1.1% [-1.2% - 3.4%]	0.37
	control	12% [13%]	14% [13%]	11% [14%]	9% [11%]		
Anxiolytics	intervention	14% [10%]	15% [10%]	16% [11%]	18% [9%]	1.6% [-0.5%- 3.6%]	0.13
	control	15% [11%]	19% [13%]	15% [11%]	14% [12%]		
NPI total severity	intervention	6.4 [2.9]	5.4 [3.8]	6.5 [3.8]	6.4 [3.0]	0.3 [-0.2 - 0.8]	0.24
	control	6.3 [2.1]	5.9 [2.3]	5.7 [2.5]	5.4 [2.4]		
NPI total distress	intervention	5.0 [3.8]	4.0 [3.9]	6.1 [5.7]	5.0 [3.8]	0.1 [-0.5 - 0.8]	0.69
	control	5.2 [3.3]	5.1 [2.9]	5.6 [3.2]	4.6 [3.3]		
CMAI total	intervention	44.0 [6.3]	44.1 [8.9]	46.4 [9.9]	46.6 [7.7]	0.6 [-0.9 - 2.1]	0.45
	control	44.1 [5.7]	43.5 [7.2]	44.0 [7.2]	44.6 [10.4]		

* Any: any antipsychotic, antidepressant, hypnotic, and/or anxiolytic

Abbreviations: SD: standard deviation; GDS: Global Deterioration Scale; DSCU: dementia special care unit; NPI-Q Neuropsychiatric Inventory – Questionnaire; CMAI: Cohen-Mansfield Agitation Inventory

Theoretical ranges of instruments: NPI-Q severity: 0 – 36; NPI-Q distress: 0 – 60; CMAI: 29 – 203.

Table 3. Results of the sensitivity analyses

	Results without organization not adhering to intervention procedures		Results without organizations already conducting medication reviews	
Variable	**Difference in slopes per 6 months [95% CI]**	**p**	**Difference in slopes per 6 months [95% CI]**	**p**
Any psychotropic drug*	3.6% [0.4%- 6.8%]	0.03	4.7% [0.8% - 8.7%]	0.02
Antipsychotics	1.5% [-1.4% - 4.3%]	0.31	1.2% [-2.6% - 5.0%]	0.53
Antidepressants	0.1% [-3.0% - 3.2%]	0.95	2.4% [-1.1 %- 6.0%]	0.17
Hypnotics	0.2% -2.2% - 2.6%]	0.88	1.9% [-1.4% - 5.2%]	0.26
Anxiolytics	1.4% [-0.7% - 3.6%]	0.19	0.4% [-2.3%- 3.2%]	0.77

* Any: any antipsychotic, antidepressant, hypnotic, and/or anxiolytic

Discussion

We found that the PROPER intervention did not reduce the prescription of antipsychotics, antidepressants, hypnotics, nor anxiolytics for neuropsychiatric symptoms in nursing home patients with dementia. The prescription of psychotropic drugs increased in the intervention group, whereas it decreased in the control group. The occurrence of neuropsychiatric symptoms remained stable. Results were consistent when we excluded data from the organization that did not fully adhere to the intervention procedures, and from organizations in the control group that carried out similar medication reviews as part of their usual care. This implies that it is disputable whether the PROPER intervention is an effective tool for reducing the prescription of psychotropic drugs.

When interpreting the results, we are able to differentiate between two potential sources for the negative effectiveness: trial conduct and the intervention's design.

Trial conduct

First, the drop-out rate in the intervention group was almost twice as high as in the control group. Although this was partly due to drop-out of one organization, there was still a substantially higher drop-out after baseline in the intervention group. Assuming that this was not a result of the intervention, it may very well have biased the effect of the intervention. For instance, the influx of new patients is likely to have missed the effect of the first medication review round, whereas the effect on prescriptions for patients that died between the assessments is not included. In general, it could very well be that changes in the case mix of the study population

had more impact on the prescription rates than the intervention. Reflections of these changes may be visible in the fluctuations between the different assessments, and may even be accountable for the negative effectiveness.

Second, we were unable to operationalize the correction for the occurrence of neuropsychiatric symptoms throughout the study in the analyses. Knowing that neuropsychiatric symptoms are the most important factor for prescription of psychotropic drugs, we would have preferred to include these in our model [23]. However, this would have raised the issue of how to operationalize this correction. The total NPI score for instance, includes a variety of symptoms [24]. The lack of correction for neuropsychiatric symptoms may have contributed to the negative effectiveness.

Third, it is interesting that the current results do not match the positive findings on the primary outcome. The PROPER intervention proved to be effective in improving the appropriateness of the drug prescriptions [13]. This implied that there was an improvement in the evaluation (i.e. the use of the drug was evaluated with a specified timeframe after the start, and this was documented in the medical file), and on the duration (i.e. the duration of use was not longer than recommended in the guideline, or a dose reduction was documented in the medical file) [25]. This illustrates that conscious decisions per individual drug do not necessarily lead to a reduction in the prescription of psychotropic drugs.

Intervention design

First, the PROPER intervention does not target all types of factors that contribute to the prescription of psychotropic drugs. We know from the previously conducted qualitative part of the PROPER study, that four themes are relevant in the prescription process [26]. These themes do not only refer to psychotropic drugs, but also to the underlying cause for prescription, i.e. the neuropsychiatric symptoms: 1) *mindset*, which comprises personal feelings, ideas and attitudes; 2) *knowledge and experience*, which reflect, for instance, level of training and number of years of employment; 3) *communication and collaboration*, covering all interactions between physicians, nurses, other professionals, and family, and 4) *external possibilities/limitations*, which comprises factors on the community level. The PROPER intervention mainly addresses the knowledge component and focuses on psychotropic drugs, rather than on neuropsychiatric symptoms. Indeed, interventions with a broader scope including improving communication, seemed effective in reducing the prescription of antipsychotics [9, 27, 28], and interventions that aimed for early detection and treatment of neuropsychiatric symptoms, appear more successful in the reduction of psychotropic drug use [29, 30]. In addition, a recent systematic review showed that psychosocial interventions initiating a culture or process change in which the physician is involved, are most effective in reducing antipsychotic prescription in nursing homes [31].

Second, the study is conducted in a timeframe in which awareness of the prescription of psychotropic drugs is already high. Organizations that applied for participation in the study may

have had an even higher awareness, leaving only a limited window for improvement. Medication review, including with nurses present, is increasingly becoming usual care, which makes the contrast between the intervention and usual care less profound. This is illustrated by the number of control organizations that had already conducted medication reviews in the presence of a nurse. Counterintuitively, the sensitivity analysis excluding these three organizations, showed that the control group showed an even larger decline in the prescription of any psychotropic drugs. In addition, even control organizations may benefit from participation in the trial due to the attention for psychotropic drug prescription, i.e. the Hawthorne effect [32].

Strengths of our study are the randomized controlled design and the substantial number of participants. However, there were also some limitations. First, some organizations had a small number of patients per DSCU, which means that prescription changes of individual patients and underlying changes in the case mix could have had a significant impact on the DSCU's psychotropic drug prevalence rates. The ranges of the number of patients per DSCU were, however, comparable for the intervention and control groups, and the composition with regard to the descriptive variables also remained similar during the study (results not shown). Second, we had some baseline imbalances that may have biased the effects: the stage of dementia (which was more severe in the intervention population) and the breakdown of the dementia types. The baseline imbalances may have resulted from the cluster randomization, which is known to be prone to selection bias and subsequent baseline imbalances [33]. Both the stage and type of dementia are expected to be correlated with the extent of neuropsychiatric symptoms [34]. However, since there were no relevant baseline imbalances for the NPI-Q and CMAI scores, we suppose that the differences in dementia stage and type did not affect the results. Third, one intervention organization did not fully adhere to the intervention procedures. However, the sensitivity analysis excluding this organization did not show different results.

Conclusion

We conclude that the PROPER intervention failed to demonstrate effectiveness in reducing the prevalence of psychotropic drugs. It may be interesting to enrich the intervention with components that address personal attitudes and communication between nursing home professionals, not only with respect to the prescription of psychotropic drugs, but also to neuropsychiatric symptoms.

References

1. Selbaek, G., K. Engedal, and S. Bergh, *The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: a systematic review.* J Am Med Dir Assoc, 2013. **14**(3): p. 161-9.
2. Ballard, C. and J. Waite, *The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease.* Cochrane Database Syst Rev, 2006(1): p. CD003476.
3. Ray, W.A., et al., *Reducing antipsychotic drug prescribing for nursing home patients: a controlled trial of the effect of an educational visit.* Am J Public Health, 1987. **77**(11): p. 1448-50.
4. Avorn, J., et al., *A randomized trial of a program to reduce the use of psychoactive drugs in nursing homes.* N Engl J Med, 1992. **327**(3): p. 168-73.
5. Crotty, M., et al., *An outreach geriatric medication advisory service in residential aged care: a randomised controlled trial of case conferencing.* Age Ageing, 2004. **33**(6): p. 612-7.
6. Westbury, J., et al., *An effective approach to decrease antipsychotic and benzodiazepine use in nursing homes: the RedUSe project.* Int Psychogeriatr, 2010. **22**(1): p. 26-36.
7. Tjia, J., et al., *Dissemination of Evidence-Based Antipsychotic Prescribing Guidelines to Nursing Homes: A Cluster Randomized Trial.* J Am Geriatr Soc, 2015. **63**(7): p. 1289-98.
8. Fossey, J., et al., *Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial.* BMJ, 2006. **332**(7544): p. 756-61.
9. Ballard, C., et al., *Impact of Antipsychotic Review and Nonpharmacological Intervention on Antipsychotic Use, Neuropsychiatric Symptoms, and Mortality in People With Dementia Living in Nursing Homes: A Factorial Cluster-Randomized Controlled Trial by the Well-Being and Health for People With Dementia (WHELD) Program.* Am J Psychiatry, 2016. **173**(3): p. 252-62.
10. Koopmans, R.T.C.M., M. Pellegrom, and E.R. van der Geer, *The Dutch Move Beyond the Concept of Nursing Home Physician Specialists.* J Am Med Dir Assoc, 2017. **18**(9): p. 746-49.
11. Smalbrugge, M., et al., *Guideline problem behavior*, in 2008: Utrecht.
12. *Nederlands Huisartsen Genootschap - Multidisciplinaire richtlijn Polyfarmacie bij ouderen*. 2012; Available from: www.nhg.org/themas/artikelen/mdr-polyfarmacie-bij-ouderen.
13. van der Spek, K., et al., *The effect of biannual medication reviews on the appropriateness of psychotropic drug use for neuropsychiatric symptoms in patients with dementia: a randomised controlled trial.* Age Ageing, 2018. **47**(3): p. 430-437.
14. Smeets, C.H., et al., *Improving psychotropic drug prescription in nursing home patients with dementia: design of a cluster randomized controlled trial.* BMC Psychiatry, 2013. **13**(1): p. 280.
15. Instituut voor Verantwoord Medicijngebruik. [cited 2018 10 Dec]; Available from: http://www.medicijngebruik.nl/.
16. Gallagher, P., et al., *STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation.* Int J Clin Pharmacol Ther 2008. **46**(2): p. 72-83.
17. Nordic Council on Medicines, *Guidelines for ATC classification*. 1990, WHO Collaborating Center for Drugs Statistics Methodology: Oslo.

18. Kaufer, D.I., et al., *Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory.* J Neuropsychiatry Clin Neurosci, 2000. **12**(2): p. 233-9.
19. Cohen-Mansfield, J., M.S. Marx, and A.S. Rosenthal, *A description of agitation in a nursing home.* J Gerontol, 1989. **44**(3): p. M77-84.
20. Zuidema, S.U., et al., *Psychotropic drug prescription in nursing home patients with dementia: influence of environmental correlates and staff distress on physicians' prescription behavior.* Int Psychogeriatr, 2011. **23**(10): p. 1632-9.
21. Reisberg, B., et al., *The Global Deterioration Scale for assessment of primary degenerative dementia.* Am J Psychiatry, 1982. **139**(9): p. 1136-9.
22. World Medical Association, *Declaration of Helsinki: ethical principles for medical research involving human subjects.* JAMA, 2013. **310**(20): p. 2191-4.
23. Smeets, C.H., et al., *Psychotropic drug prescription for nursing home residents with dementia: prevalence and associations with non-resident-related factors.* Aging & Mental Health, 2017: p.1-9.
24. Smeets, C.H.W., et al., *Efficacy of antipsychotics in dementia depended on the definition of patients and outcomes: a meta-epidemiological study.* J Clin Epidemiol, 2018. **101**: p. 17-27.
25. van der Spek, K., et al., *A reliable and valid index was developed to measure appropriate psychotropic drug use in dementia.* J Clin Epidemiol, 2015. **68**(8): p. 903-12.
26. Smeets, C.H., et al., *Factors Related to Psychotropic Drug Prescription for Neuropsychiatric Symptoms in Nursing Home Residents With Dementia.* J Am Med Dir Assoc, 2014. **15**(11): p. 835-840.
27. Tjia, J., et al., *Association of a Communication Training Program With Use of Antipsychotics in Nursing Homes.* JAMA Intern Med, 2017. **177**(6): p. 846-853.
28. Ballard, C., et al., *Brief psychosocial therapy for the treatment of agitation in Alzheimer disease (the CALM-AD trial).* Am J Geriatr Psychiatry, 2009. **17**(9): p. 726-33.
29. Rapp, M.A., et al., *Agitation in Nursing Home Residents With Dementia (VIDEANT Trial): Effects of a Cluster-Randomized, Controlled, Guideline Implementation Trial.* J Am Med Dir Assoc, 2013. **14**(9): p. 690-5.
30. Zwijsen, S.A., et al., *Coming to grips with challenging behavior: a cluster randomized controlled trial on the effects of a multidisciplinary care program for challenging behavior in dementia.* J Am Med Dir Assoc, 2014. **15**(7): p. 531 e1-531 e10.
31. Birkenhager-Gillesse, E.G., et al., *Effects of Psychosocial Interventions for Behavioral and Psychological Symptoms in Dementia on the Prescription of Psychotropic Drugs: A Systematic Review and Meta-Analyses.* J Am Med Dir Assoc, 2018. **19**(3): p. 276.e1-276.e9.
32. Sedgwick, P. and N. Greenwood, *Understanding the Hawthorne effect.* Bmj, 2015. **351**: p. h4672.
33. Bolzern, J., et al., *A review of cluster randomized trials found statistical evidence of selection bias.* J Clin Epidemiol, 2018. **99**: p. 106-112.
34. Caputo, M., et al., *Neuropsychiatric symptoms in 921 elderly subjects with dementia: a comparison between vascular and neurodegenerative types.* Acta Psychiatr Scand, 2008. **117**(6): p. 455-64.

Verzorgende: Er zijn mensen [...] die het heel erg belangrijk vinden omdat ze dan verschil zien bij hun moeder of vader. [...] Er is bijvoorbeeld ook een: 'Kan je niet 'zo nodig' medicatie geven want ze zit al de hele tijd te roepen?' [...] Dus dan vind ik dat wel heel lastig. Geef ik? Wie bepaalt nou dat zij dit krijgt?

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Chapter 8

General discussion

This chapter starts with addressing the research questions. Then proper prescription will be put in perspective, and it ends with implications and conclusions.

Research questions

1. *Which factors are involved in the prescription of psychotropic drugs for neuropsychiatric symptoms in patients with dementia?*

Chapter 3 answers this question from a qualitative perspective. Interviews with physicians and nurses gave input for the development of a conceptual framework with four themes related to the psychopharmacological treatment of neuropsychiatric symptoms: *mindset* (beliefs and attitudes of the stakeholders), *knowledge and experience* (what stakeholders know and are capable of), *communication and cooperation* (interactions leading to teamwork), and *external possibilities/limitations* (preconditions on institutional and national level). Next to the apparent topic 'prescription of psychotropic drugs', neuropsychiatric symptoms turned out to be equally important. Also, discontinuation of previous prescriptions was found to deserve attention. In chapter 4, the potential factors fitting into this framework were investigated using a cross-sectional study design. From 26 non-patient-related factors, only two showed a statistically significant association. Although it is expected that 5% of the associations is due to chance, it is remarkable that both were connected to *communication*. Further, it was interesting that neuropsychiatric symptoms and related distress were most clearly associated with prescription rates. Chapter 5 illustrates that the pooled effect sizes of antipsychotics in reviews are subject to methodological decisions regarding eligibility criteria . This can be seen as an example of progressing insights in *knowledge and experience* that contribute to the decision whether or not to start or stop the prescription of psychotropic drugs.

2. *Is structured and repeated multidisciplinary medication review effective in reducing psychotropic drug prescription?*

Chapter 7 shows that the PROPER intervention consisting of structured and repeated medication reviews conducted by a team of a physician, nurse, and pharmacist, did not reduce the prescription rates of psychotropic drugs. This may be related to the fact that the PROPER intervention was too narrow given the broad spectrum of factors that were found to contribute to prescription.

Proper prescription in perspective

The answers to the research questions indicate that the prescription of psychotropic drugs is complex and should be regarded in a broader context. In this paragraph, the findings will be discussed and related to literature. This is an attempt to put prescription into perspective and to take a step forward in finding new angles to improve the psychopharmacological treatment of neuropsychiatric symptoms.

The complex context of prescription

Our findings illustrate that there are many aspects toward the prescription of psychotropic drugs. The subjective need for treatment of neuropsychiatric symptoms and the subsequent decision to (de)prescribe psychotropic drugs is complex. Below, this complexity will be illustrated in terms of the concepts of our framework.

Mindset

The *mindset* reflects that all stakeholders have their own point of view on the necessity to treat neuropsychiatric symptoms and on whether psychotropic drugs are a potentially desirable solution. The qualitative PROPER data showed that not only the patient is a stakeholder in the prescription. There are many others who in some way also have an interest: next of kin, other patients, nurses, the physician, the psychologist, other healthcare professionals, as well as all others who surround the patient. With regard to the need to treat neuropsychiatric symptoms, not only each of them may have a view on the distress for the patient, but also for other stakeholders, and – maybe even subconsciously – for themselves. A daughter, for instance, may think 'my father would never have wished to behave this agitated', be afraid that he would hurt the nurses, and feel ashamed about his behavior. The nurse may feel sorry for this patient who suffers from his agitation, consider that other patients should be protected for his behavior, and experience irritation due to the extra time that she needs to manage the agitation. Similarly, all stakeholders may have opinions on the pros and cons of prescribing psychotropic drugs. For instance, next of kin could consider the risk of side effects acceptable in the final phase of life. Physicians may have an interest to follow guidelines, or be sensitive to the critical assessment of their prevalence rates by colleagues or nursing home management. The views of these stakeholders might be colored by emotional, environmental, organizational, and societal issues such as the relation with the patient, the ability to cope with neuropsychiatric symptoms, the attitude toward medication, medical knowledge, and previous experiences with prescription [1, 2].

Of all stakeholders, the patient is, of course, the most important. Patient's preferences indeed constitute one of the three pillars of evidence-based medicine, aside from clinical evidence and clinical expertise [3]. However, among people with dementia, the patient's preferences are not self-evident. Especially people with advanced dementia, who were studied in this thesis, cannot express their preferences and needs themselves usually. Those who represent these patients, may be colored in their views. Next of kin appear to see the patient as the person he or she was prior

to the dementia [4]. Therefore, they may regard the preferences of their partner, father etcetera as the wishes of the person before the dementia. In contrast, care personnel usually do not know the patient prior to the dementia, and only relate to the patient in the current state. This illustrates the difficulty to consider the actual patient's preferences regarding prescription properly.

Knowledge and experience

Knowledge and experience includes the views on prescription related to (scientific) facts and the possibility to exert skills. It regards what stakeholders know and what they are capable of, and is influenced by beliefs. *Knowledge and experience*, especially the knowledge that comes from clinical trials, has received by far the most attention in the literature regarding prescription of psychotropic drugs, and also in the design of the PROPER study.

Looking at *knowledge*, it seems straightforward to treat patients based on the evidence from randomized controlled trials and meta-analyses. The Verenso Guideline has assembled the evidence and appeared to be a common source for the physicians in our study to decide upon prescription. The previous version of this guideline had a central role in the PROPER study in two ways [5]. First, the Verenso guideline was used to develop a new instrument for assessing the primary outcome of the PROPER study, the Appropriate Psychotropic drugs use In Dementia (APID) [6]. Results related to the APID index are described in the thesis of Van der Spek [7]. Second, one of the main components of the PROPER intervention was adherence to the Verenso guideline [8]. From the *knowledge* viewpoint, prescription should be limited to specific psychotropic drugs for certain indications for a limited duration, taking into account interactions with comorbidities and use of other drugs.

However, in daily practice, prescribing based on scientific evidence was experienced as inconvenient for physicians in our qualitative study. They felt discomfort with regard to guideline adherence on a few points [2]. First, they mentioned the difficulty to predict the chance on effect and risk of side effects for individual patients using group evidence. Second, they brought up the limited generalizability. They perceived that there are few data from the population of nursing home patients with dementia, let alone from subgroups such as patients with Lewy body disease. This is also what we found: postulating that evidence on specific neuropsychiatric symptoms should come from populations having these symptoms, data are even more scarce [9]. Third, the interviewees mentioned that they had limited confidence in the clinical evidence since they believed that the mechanisms of action of psychotropic drugs are mostly unknown. Fourth, they considered that most evidence comes from trials that may be biased due to the financial interest of pharmaceutical companies. These four topics were also recently mentioned in a report by the 'Raad voor Volksgezondheid en Samenleving' (RVS) that points at the limitations of evidence-based medicine and is currently under debate [10]. Interviewees perceived these subjects as impeding a decision upon proper prescription. They may on the one hand limit prescription (there is hardly evidence), but especially the first two points may on the other hand also facilitate prescription (absence of evidence is no evidence for absence of effect). These critical viewpoints

are in line with the current developments regarding personalized medicine and n=1 trials and may explain why physicians sometimes opt for a motivated deviation from prescription according to the Verenso guideline [11].

Looking at *experience*, neuropsychiatric symptoms, being the underlying reason for prescription, are most eye-catching. The Verenso guideline for example stipulates that prior to psychopharmacological treatment, all other options should have been explored first. These options include prevention and psychosocial treatment, but also acceptance of neuropsychiatric symptoms to a certain level. Our qualitative findings revealed that the exploration of other options often not succeeds due to lack of sufficient education, experience, and skills to know what to do. The last is in literature described as tacit knowledge [12]. For instance nurses who know that dementia usually comes with behavioral changes, that specific conditions can trigger neuropsychiatric symptoms, and how they can distract patients from what causes their behavior, may in certain situations avoid that psychopharmacological treatment comes into sight. However, the ability to make full use of *experience* may be hampered by resource issues, such as lack of continuity in care personnel and available time.

The *knowledge* factors have a rather rational nature, which may evoke a suggestion of objectivity. However, they do not always give an univocal interpretation of proper prescription. The qualitative study gave two examples explaining this. First, our interviewees consistently mentioned to be reluctant in prescribing antipsychotics due to the side effect sedation. Yet, prior to receiving the label 'chemical fixation', sedation was presented as a desired effect [13]. Sedation can also erroneously be interpreted as a positive effect. This may be the reason why some nurses believe that antipsychotics are a quick solution to resolve neuropsychiatric symptoms. This would explain the frequently reported request of nurses for prescription [14-17]. Second, some interviewees expressed their concern that adherence to the Verenso guideline may not just limit prescription to those drugs that have scientifically been proven to be effective. They mentioned that the guideline could also be misused as a license to prescribe, provided that there was evidence for effect on the target symptom. The viewpoint that guideline adherence does not automatically imply best care, was also described in the RVS report [10].

Communication and cooperation

Communication and cooperation comprises all viewpoints that are connected to interactions between the stakeholders. *Communication* and the closely related *cooperation* (from now on in short *communication*) showed to play a crucial role in the prescription of psychotropic drugs in the qualitative study. The quality and frequency of interactions between all stakeholders including openness, addressing topics for discussion, and sharing knowledge and ideas, were found to contribute to prescription. Since *communication* occurs between all stakeholders, there are many possible 'communication lines' for one patient: between patient and nurse, physician and nurse, between nurses, between psychologist and nurse, between relatives and physician, relatives and nurse, with other care personnel, etcetera. Nursing homes usually have various formal multidisciplinary

meetings regarding treatment goals ('artsenvisite', between physician and nurse; and 'multidisciplinair overleg (MDO)' with additional healthcare professionals and possibly patient or representative), specifically regarding behavior ('gedragvisite' or 'omgangsoverleg') or regarding drug safety with the pharmacist ('farmacotherapeutisch overleg') [18]. There are of course also transfers between nurses' shifts, informal conversations and often, written communication appears to be used. The qualitative results indicate that in case of suboptimal communication, it seems easier to opt for psychopharmacological treatment.

Communication with and between nurses deserves special attention. From all non-residential stakeholders, nurses are in closest and most frequent contact with the patients. Therefore, they have to deal with neuropsychiatric symptoms most continuously [19]. They may or may not perceive and judge behavior as disturbing and thus requiring some kind of treatment. Since they choose whether or not to pass this information to the physician and other stakeholders, they bear a large part of the responsibility regarding prescription. In case they attempt to deal with symptoms by themselves too long, and the behavior escalates, this may result in a prescription that might have been avoidable. Nurses may also want to provide some kind of a solution to a patient who clearly suffers from neuropsychiatric symptoms [20]. Further, nurses have a special responsibility with regard to pro re nata prescriptions [21]. Studies show that there may be quite some pro re nata prescriptions [22]. Most nursing homes have formal communication procedures between nurses to coordinate the actual dispense. Communication with and between nurses thus has a direct impact on the decision whether a patient is given (pro re nata) psychotropic drugs.

For proper prescription, *communication* between all stakeholders and regarding all factors, seems indispensable according to our qualitative findings [2]. Interaction on *mindset* issues may give mutual understanding of why other stakeholders have certain opinions pro or contra prescription. Communication regarding the sharing of knowledge may help to improve prescription. Especially sharing knowledge on prevention or early addressing neuropsychiatric symptoms regarding specific patients, is considered to contribute to less prescriptions [2]. Individual stakeholders may have specific knowledge that is not necessarily known to all others. For instance, if one nurse manages certain behavior more adequately than another, and she shares what she does to achieve this, this may prevent prescription. Similarly, family may have ideas on how to avoid or treat neuropsychiatric symptoms for a specific patient. Communication also appeared important with regard to the capacity of nurses to cope with behavior. Further, if physicians share their pharmacological knowledge, they may more easily persuade nurses with limited knowledge on side effects, in the decision not to prescribe. Moreover, communication may be helpful to tackle certain *external limitations* such as workload issues or access to psychologists.

The importance of *communication* with regard to prescription is supported by several recent publications. A systematic review of qualitative studies on the prescription of antipsychotics, in which our study was included, addressed communication and collaboration as a key concept [23]. Moreover, effective communication between staff was found to be an important factor contributing to appropriate prescription [24]. Also the success rate of medication reviews to improve psychotropic drug prescription seems related to social and professional interactions [25]. Unfortunately, it appears that communication between health care professionals regarding neuropsychiatric symptoms is frequently suboptimal [19]. It is therefore important that all healthcare professionals are aware that improving *communication* may provide opportunities to improve prescription.

External possibilities/limitations

External possibilities/limitations regards mainly the background of preconditions on institutional and national level. Particularly the obstacles that the stakeholders run into, but also the opportunities they use. Our findings illustrate that nursing homes make up the frame in which most of these factors take place. The nursing home culture is considered to be related to psychotropic drug prescription [26-29]. A recent model attempted to capture this culture [30]. According to this model, aside from factors such as staffing issues and meeting structure, underlying factors including teamwork and having an eye for individual patients, and a core layer regarding values and beliefs, are considered to contribute to prescription [31]. The description of this core layer comes close to what we called *mindset* in our framework, which implies that there may be a kind of a 'nursing home mindset'. On the institutional level, staffing issues are most striking. Our qualitative findings indicated that high workload, lack of continuity, and insufficient (tacit) knowledge of especially nurses may lead to avoidable psychotropic drug prescriptions [2]. This finding is supported by several studies [32-34]. Insufficient time and lack of continuity of healthcare professionals may affect all above-described factors and will therefore have consequences for prescription.

The quality of long-term care received much attention from the Dutch government in the past years. Various attempts have been and are still being made to improve quality of care, by means of programs such as 'Waardigheid en trots', the 'Kwaliteitskader Verpleeghuiszorg', and 'Thuis in het verpleeghuis, Waardigheid en Trots op elke locatie' [35-37]. Another program specifically aims to improve psychotropic drug prescription: 'Beter af met minder' including 'Reduction of Inappropriate psychotropic Drug use in nursing home residents with dementia (RID)' [38, 39]. Also, legislation has been revised. In 2015 a new law came into effect, the 'Wet Langdurige Zorg', and as of 2020 the 'Wet Zorg en Dwang' will be in force [40, 41]. These developments imply that prevalence rates of antipsychotics should be registered, and that a detailed step-by-step process must be followed prior to prescribing drugs for neuropsychiatric symptoms [37, 41]. Furthermore, the Health and Youth Care Inspectorate has phrased eight key elements with regard to neuropsychiatric symptoms in dementia that stipulate a multidisciplinary approach

involving next of kin, prevention and nonpharmacological treatment. If psychotropic drugs are prescribed, this should be done only according to guidelines, and with biannual evaluations [42].

These national initiatives within the *external possibilities/limitations* may facilitate more proper prescription. Not only do they stress to have an eye for the needs and wishes of individual patients, they also emphasize the empowerment of healthcare professionals. They stipulate that the confidence in healthcare professionals to make use of their skills needs to be strengthened, and that professionals should get more time for individual patients. The latter should be facilitated by employing sufficient numbers and sufficiently educated personnel [37]. The budget for nursing home care was enlarged with 2.1 billion euro yearly, of which 85% must be spent on extra personnel [43]. Unfortunately, these initiatives did not yet relieve the workload. A recent report showed that 69% of nurses (23% of whom working in the nursing homes) feel that the workload has actually increased [44].

The previous paragraphs show that many closely related and interactive factors are associated with the prescription of psychotropic drugs. These factors constitute the complex context in which prescription occurs. Prescription should therefore always be regarded within its context.

Judging prescription

Prescription within its context easily provokes an opinion on whether it should be judged as proper, or not. Stakeholders may have opinions on proper prescription that may be valid within (a part of) the context and there are preconditions against which these opinions occur. Prescriptions can be fully in line with the Verenso guideline, and be still not perceived as proper. For instance, this may happen when a nurse tacitly knows that a patient would benefit from some extra attention or a joint walk outside which she cannot give, or when a nurse has no time to update the nurse of the next shift about a situation that triggered behavior. Similarly, it may be completely correct not to prescribe since there is no evidence, whereas it may be perceived as withholding a chance on relief. For example, when a patient suffers from neuropsychiatric symptoms in the final phase of life, and risks of side effects may be seen as less important. Prescriptions may also be difficult to judge when it comes to the question who can best represent the patient's preferences regarding prescription, and who can most consciously bring together and balance the opinions of all stakeholders. These dilemmas illustrate that prescription involves balancing norms and values.

Frequently, prescription is judged on a group level. In order to get some insight into prescription, researchers, the Health and Youth Care Inspectorate, nursing home management, but also physicians, tend to use measurable data. Prevalence rates of drug prescriptions are commonly used for this purpose. We have also assessed these in the PROPER study. These rates are easy to obtain but they are biased by many factors including neuropsychiatric symptoms and psychiatric comorbidities. In turn, these factors are subject to changes in the long-term care. For instance, neuropsychiatric symptoms may have become more common in the current nursing

home population due to a reform of long-term care legislation [45]. Even though psychotropic drug prevalence rates must be interpreted with caution, they are useful to oversee time trends. This is what we also did when we concluded that the prescription of antipsychotics appeared to decrease, and the prescription of other psychotropic drugs to remain rather stable [46].

Aside from prevalence rates, also measures are applied that attempt to assess the appropriateness of prescription, such as the Beers and STOPP/START criteria [47, 48]. Also, local guidelines are used in studies to judge the appropriateness of prescription [49-53]. As described above, within the PROPER study the Dutch APID was developed [6]. The APID uses seven items to assess the appropriateness of prescription: indication, evaluation, dose, drug-drug interactions, contra-indications, duplications, and duration. Although these measures for appropriateness include much more nuance, they do not take into account the full context. There may be valid reasons to deviate from guidelines within the context, that are not easily caught by these instruments. This may, at least partly, explain why only 10% of the psychotropic drugs was judged to be prescribed appropriately in our study sample [54].

Considering the complex context outlined above, proper prescription implies that a judgment is made between all pros and cons, while weighing carefully the interests of all those concerned. And if this leads to a prescription, the judgment should not be limited to the start, but also to the end, and to every single moment in between when a patient receives the drug. Due to this complexity, it is questionable whether proper prescription can actually be measured, and what the risks are when results are interpreted outside the context.

Improving prescription

For improving prescription, it may be similarly necessary to address the context as comprehensively as possible. We found that the PROPER intervention did not reduce the frequency of psychotropic drug prescription (Smeets, submitted). This might be due to the fact that medication reviews were commonly conducted by nursing homes in the control arm. But it could also be due to the fact that the intervention was too narrow given the complex context.

Others have also been searching for strategies to improve, actually mainly to reduce, the prescription of psychotropic drugs. Recently, a systematic review was conducted on interventions including education, in reach services or culture/process changes, that aimed to reduce the occurrence of neuropsychiatric symptoms [55]. Those interventions using elements that we would have categorized as *knowledge* in our qualitative framework, were not effective in reducing prescriptions. In contrast, those that used a broader approach, addressing elements that could be categorized under *mindset* and *communication and cooperation* additionally, were effective in reducing antipsychotic, but not antidepressant prescriptions. Among the studies with a broader approach were also two Dutch trials: GRIP was effective in reducing antipsychotics and antidepressants; STA-OP only in reducing antidepressants [56, 57]. Two trials with a broad approach were published afterwards: COSMOS reduced the use of psychotropic drugs, TIME

did not [58, 59]. Interventions that aimed at improving prescription particularly, with merely *knowledge* elements, were partly effective [60-63], and partly not [64, 65]. Studies with non-controlled designs with a focus on psychotropic drugs using *knowledge* were either positive [66], or negative [67, 68]; those addressing additional components were positive [69-71]. There was one non-controlled study with a follow-up that had a broad approach and used more components which had positive results [72, 73]. These studies corroborate that interventions which address not only *knowledge* but also *mindset* and *communication*, are more likely to reduce prescription.

When attempting to address the full context, this would regard *mindset*, *knowledge*, *communication*, as well as the *external possibilities/limitations*. From these themes, *communication* may be the most accessible and susceptible to change. Since it is also clearly connected to the other themes, it could be a suitable starting point for improving (de)prescription. It may be interesting to talk more extensively about the *mindset* (opinions, preferences, feelings of the patient and other stakeholders), about *knowledge* (with a focus on sharing information and addressing knowledge gaps), about *communication* itself (quality and frequency of interactions between the stakeholders), and about *external possibilities/limitations* (obstacles that prevent proper prescription). Although this last theme is beyond the reach of most physicians and nurses, it may be wise to openly discuss whether certain obstacles hamper proper prescription. Enhancing *communication* to address the context comprehensively, may therefore contribute to proper prescription.

Evidently, *communication* is already used to balance all factors pro and contra prescription between stakeholders. But there appears a to be window for doing this more explicitly. For very complex cases in which prescription of psychotropic drugs is considered, it is becoming more common to have a moral deliberation [74]. This is a structured group discussion about a moral question under guidance of a chairperson. For less complicated cases, a light version may be interesting. Recently, an interesting framework was developed for the nursing home setting, that may be supportive. This framework aims to 'clarify and articulate the thinking process of the physician' and has an eye for both the existence and the weighing of stakeholders' views, including patients with dementia [75]. The framework uses four questions: 1) What is known about the patient's aims and preferences? 2) Will the intervention be effective? 3) Will the intervention support the aims and preferences of the patient? 4) In view of the aims and preferences, do the benefits outweigh the risks? Due to its simplicity, this framework could be very useful to take into account the full context as described in this thesis, as a practical alternative for all cases where prescription is considered. It may be even supplemented with an evaluation with hindsight [76].

Implications

There is evidence for lack of effect of psychotropic drugs, and there is evidence for enlarged risks of side effects. However, under certain circumstances, prescription may still seem a solution. In these situations, it comes to addressing the full context: is it proper to prescribe psychotropic drugs for that specific situation?

For researchers, it may be interesting to regard research questions related to this topic from philosophy and social sciences, in addition to medical sciences. These sciences might provide a different view on ways to address the full context, which could be interesting to develop interventions and measures to assess the effect of interventions. Also, it is needed to investigate the opinions that are currently (relatively) understudied such as views from patients themselves, next of kin, psychologists, nursing home management and policy makers and subsequently to explore methods for balancing stakeholders' views and shared decision-making. Researchers should have an eye for developments of personalized medicine and n=1 trials but also to stand up for the risk that evidence-based medicine and guidelines are dismissed as 'just an opinion'.

For healthcare professionals including physicians, nurses, and psychologists, it may be prudent to focus on communication for improving prescription. They may seek for ways to speak more openly about avoiding neuropsychiatric symptoms, addressing them early and about psychosocial treatment options. They should address differences in viewpoints, feelings of dissatisfaction and powerlessness, and subsequently talk about the morally best treatment option. This could also include to have an eye for the dilemmas regarding the patient's preferences in a severe stage of dementia and regarding sedation. The communication should not be limited to prevention or new prescriptions; also earlier decisions should be evaluated. For situations where (continued) prescription is seriously considered, a thoughtful decision approach could be adopted as suggested in the literature [75]. Alternatively, it should at least be clear why individual stakeholders opt for prescription, since this reason may indicate the ultimate topic to be resolved. It is needed that healthcare professionals take sufficient time for talking with each other – both between disciplines, and between professionals with more and less experience – with patients, and with relatives. Further, they should involve nursing home management when appropriate, as these managers may have more options to fulfill the requirements for proper prescription.

Policy makers and nursing home management could have an important role in facilitating all communication and teamwork that is deemed necessary by healthcare professionals. They should facilitate a healthy nursing home mindset by encouraging healthcare professionals to take time to talk with patients, family, and each other, and for reflection. This may include informal contact moments, but also formal meetings such as 'intervisie', team meetings, and consultation of the psychologist. In addition, it is recommended that policy makers and nursing home management support the employment of sufficient numbers and sufficiently educated care personnel. They should use the governmental budget for extra personnel thoughtfully. Further,

nursing homes could apply the policy that nursing home patients as much as possible not only have the same nurses, but also the same physician and psychologist throughout their stay. By facilitating that healthcare professionals have all options for optimal communication and for providing continuity in care, policy makers and nursing home management may substantially contribute to improving prescription.

Conclusions

This thesis aimed to explore which factors are involved in the psychopharmacological treatment of neuropsychiatric symptoms, and to reduce prescription by means of structured and repeated multidisciplinary medication reviews. It appeared that prescription is complex, and should be regarded in its context. Given the complex context, the PROPER intervention may have been too narrow to reduce prescription. Putting all findings in perspective, it may be necessary to address the context as comprehensively as possible – using communication as an important vehicle – for improving the prescription of psychotropic drugs within this vulnerable population of nursing home patients with dementia.

References

1. Walsh, K.A., et al., *Exploring Antipsychotic Prescribing Behaviors for Nursing Home Residents With Dementia: A Qualitative Study.* J Am Med Dir Assoc, 2018. **19**(11): p. 948-958.e12.
2. Smeets, C.H., et al., *Factors Related to Psychotropic Drug Prescription for Neuropsychiatric Symptoms in Nursing Home Residents With Dementia.* J Am Med Dir Assoc, 2014. **15**(11): p. 835-840.
3. Sackett, D.L., et al., *Evidence based medicine: what it is and what it isn't.* Bmj, 1996. **312**(7023): p. 71-2.
4. Davis, D.H., *Dementia: sociological and philosophical constructions.* Soc Sci Med, 2004. **58**(2): p. 369-78.
5. Smalbrugge, M., et al., *Guideline problem behavior*, in 2008: Utrecht.
6. van der Spek, K., et al., *A reliable and valid index was developed to measure appropriate psychotropic drug use in dementia.* J Clin Epidemiol, 2015. **68**(8): p. 903-12.
7. Van der Spek, K., *Appropriate psychotropic drug use in institutionalized people with dementia. The PROPER-study*. 2018.
8. Smeets, C.H., et al., *Improving psychotropic drug prescription in nursing home patients with dementia: design of a cluster randomized controlled trial.* BMC Psychiatry, 2013. **13**(1): p. 280.
9. Smeets, C.H.W., et al., *Efficacy of antipsychotics in dementia depended on the definition of patients and outcomes: a meta-epidemiological study.* J Clin Epidemiol, 2018. **101**: p. 17-27.
10. Raad voor Volksgezondheid en Samenleving, *Zonder context geen bewijs. Over de illusie van evidence-based practice in de zorg*. Den Haag.
11. Myin-Germeys, I. and B. Penninx, *[Personalised medicine: from a scientific perspective]*. Tijdschr Psychiatr, 2018. **60**(3): p. 210-214.
12. Polanyi, M., *The Tacit Dimension*. 1966, Chicago: University of Chicago.
13. Seager, C.P., *Chlorpromazine in treatment of elderly psychotic women.* Br Med J, 1955. **1**(4918): p. 882-5.
14. Almutairi, S., K. Masters, and P. Donyai, *The health professional experience of using antipsychotic medication for dementia in care homes: A study using grounded theory and focussing on inappropriate prescribing.* J Psychiatr Ment Health Nurs, 2018. **25**(5-6): p. 307-318.
15. Lemay, C.A., et al., *Knowledge of and perceived need for evidence-based education about antipsychotic medications among nursing home leadership and staff.* J Am Med Dir Assoc, 2013. **14**(12): p. 895-900.
16. Janus, S.I., et al., *Determinants of the nurses' and nursing assistants' request for antipsychotics for people with dementia.* Int Psychogeriatr, 2017. **29**(3): p. 475-484.
17. Ludwin, B.M. and S. Meeks, *Psychological factors related to nurses' intentions to initiate an antipsychotic or psychosocial intervention with nursing home residents.* Geriatric Nursing, 2018. **39**(5): p. 584-592.
18. Verenso, *Handreiking Multidisciplinair overleg (MDO)*. 2015.
19. Prins, M., C. Heijkants, and B. Willemse, *Onbegrepen gedrag in de verpleeghuiszorg voor mensen met dementie. Monitor Woonvormen Dementie*. 2018, Trimbos-instituut: Utrecht.
20. Kerns, J.W., et al., *Caregiver Perspectives About Using Antipsychotics and Other Medications for Symptoms of Dementia.* Gerontologist, 2018. **58**(2): p. e35-e45.
21. Carder, P.C., *"Learning about your residents": how assisted living residence medication aides decide to administer pro re nata medications to persons with dementia.* Gerontologist, 2012. **52**(1): p. 46-55.

22. Dorks, M., K. Allers, and F. Hoffmann, *Pro Re Nata Drug Use in Nursing Home Residents: A Systematic Review*. J Am Med Dir Assoc, 2019. **20**(3): p. 287-293.e7.
23. Walsh, K.A., et al., *Influences on Decision-Making Regarding Antipsychotic Prescribing in Nursing Home Residents With Dementia: A Systematic Review and Synthesis of Qualitative Evidence*. J Am Med Dir Assoc, 2017. **18**(10): p. 897.e1-897.e12.
24. Sawan, M., et al., *Exploring the link between organizational climate and the use of psychotropic medicines in nursing homes: A qualitative study*. Res Social Adm Pharm, 2017. **13**(3): p. 513-523.
25. Sawan, M.J., et al., *A qualitative study exploring visible components of organizational culture: what influences the use of psychotropic medicines in nursing homes?* International Psychogeriatrics, 2016. **28**(10): p. 1725-1735.
26. van der Putten, M.J., et al., *Antipsychotic drug prescription rates among Dutch nursing homes: the influence of patient characteristics and the dementia special care unit*. Aging Ment Health, 2014.
27. Peri, K., et al., *Is psychotropic medication use related to organisational and treatment culture in residential care*. J Health Organ Manag, 2015. **29**(7): p. 1065-79.
28. Kleijer, B.C., et al., *Variability between nursing homes in prevalence of antipsychotic use in patients with dementia*. Int Psychogeriatr, 2014. **26**(3): p. 363-71.
29. Zuidema, S.U., et al., *Psychotropic drug prescription in nursing home patients with dementia: influence of environmental correlates and staff distress on physicians' prescription behavior*. Int Psychogeriatr, 2011. **23**(10): p. 1632-9.
30. Sawan, M., Y.H. Jeon, and T.F. Chen, *Relationship between Organizational Culture and the Use of Psychotropic Medicines in Nursing Homes: A Systematic Integrative Review*. Drugs Aging, 2018. **35**(3): p. 189-211.
31. Sawan, M., Y.H. Jeon, and T.F. Chen, *Shaping the use of psychotropic medicines in nursing homes: A qualitative study on organisational culture*. Soc Sci Med, 2018. **202**: p. 70-78.
32. Edberg, A.K., et al., *Strain in nursing care of people with dementia: nurses' experience in Australia, Sweden and United Kingdom*. Aging Ment Health, 2008. **12**(2): p. 236-43.
33. Ellis, M.L., et al., *Assessing approaches and barriers to reduce antipsychotic drug use in Florida nursing homes*. Aging Ment Health, 2014: p. 1-10.
34. Simmons, S.F., et al., *Reducing Antipsychotic Medication Use in Nursing Homes: A Qualitative Study of Nursing Staff Perceptions*. Gerontologist, 2018. **58**(4): p. e239-e250.
35. Vilans. *Thuis in het verpleeghuis – Waardigheid en trots op elke locatie*. 3 April 2019]; Available from: https://www.waardigheidentrots.nl/.
36. Ministerie van Volksgezondheid Welzijn en Sport, *Thuis in het Verpleeghuis. Waardigheid en trots op elke locatie*. 2018.
37. Zorginstituut Nederland, *Kwaliteitskader Verpleeghuiszorg*. 2017.
38. Vilans. *Beter af met minder? Bewust gebruik psychofarmaca*. 6 March 2019]; Available from: https://www.vilans.nl/projecten/psychofarmaca-bewust-gebruiken.
39. *RID: Reduction of Inappropriate psychotropic Drug use in nursing home residents with dementia*. 27 February 2019]; Available from: https://ukonnetwerk.nl/rid.
40. *Wet langdurige zorg*. 6 March 2019]; Available from: https://wetten.overheid.nl/BWBR0035917/2019-01-01.
41. Inspectie Gezondheidszorg en Jeugd (IGJ) Ministerie van Volksgezondheid Welzijn en Sport. *Wet zorg en dwang*. 6 March 2019; Available from: https://www.igj.nl/onderwerpen/nieuwe-wetgeving/wet-zorg-en-dwang.

42. Inspectie Gezondheidszorg en Jeugd (IGJ) Ministerie van Volksgezondheid Welzijn en Sport. *Omgaan met mensen met dementie*. 26 February 2019]; Available from: www.igj.nl/zorgsectoren/verpleeghuiszorg/dementie.
43. Ministerie van Volksgezondheid Welzijn en Sport, *Voortgangsrapportage Programma 'Thuis in het Verpleeghuis, Waardigheid en Trots op elke locatie'*. 2018: Den Haag.
44. V&VN, *Personeelstekorten 1 jaar later. "Ik merk geen verschil."*. 2019.
45. Maarse, J.A. and P.P. Jeurissen, *The policy and politics of the 2015 long-term care reform in the Netherlands*. Health Policy, 2016. **120**(3): p. 241-5.
46. Smeets, C.H.W., et al., *Psychotropic drug prescription for nursing home residents with dementia: prevalence and associations with non-resident-related factors*. Aging & Mental Health, 2017: p. 1-9.
47. O'Mahony, D., et al., *STOPP/START criteria for potentially inappropriate prescribing in older people: version 2*. Age Ageing, 2015. **44**(2): p. 213-8.
48. *American Geriatrics Society 2019 Updated AGS Beers Criteria(R) for Potentially Inappropriate Medication Use in Older Adults*. J Am Geriatr Soc, 2019.
49. Laffon de Mazieres, C., et al., *Organizational Factors Associated With Inappropriate Neuroleptic Drug Prescribing in Nursing Homes: A Multilevel Approach*. J Am Med Dir Assoc, 2015.
50. Nyborg, G., et al., *Potentially inappropriate medication use in nursing homes: an observational study using the NORGEP-NH criteria*. BMC Geriatr, 2017. **17**(1): p. 220.
51. Lucas, J.A., et al., *Antipsychotic medication use in nursing homes: a proposed measure of quality*. Int J Geriatr Psychiatry, 2014. **29**(10): p. 1049-61.
52. Olsson, J., et al., *Quality of drug prescribing in elderly people in nursing homes and special care units for dementia: a cross-sectional computerized pharmacy register analysis*. Clin Drug Investig, 2010. **30**(5): p. 289-300.
53. Holt, S., S. Schmiedl, and P.A. Thurmann, *Potentially inappropriate medications in the elderly: the PRISCUS list*. Dtsch Arztebl Int, 2010. **107**(31-32): p. 543-51.
54. van der Spek, K., et al., *Only 10% of the psychotropic drug use for neuropsychiatric symptoms in patients with dementia is fully appropriate. The PROPER I-study*. Int Psychogeriatr, 2016. **28**(10): p. 1589-95.
55. Birkenhager-Gillesse, E.G., et al., *Effects of Psychosocial Interventions for Behavioral and Psychological Symptoms in Dementia on the Prescription of Psychotropic Drugs: A Systematic Review and Meta-Analyses*. J Am Med Dir Assoc, 2018. **19**(3): p. 276.e1-276.e9.
56. Zwijsen, S.A., et al., *Coming to grips with challenging behavior: a cluster randomized controlled trial on the effects of a multidisciplinary care program for challenging behavior in dementia*. J Am Med Dir Assoc, 2014. **15**(7): p. 531 e1-531 e10.
57. Pieper, M.J., et al., *Effects of a Stepwise Multidisciplinary Intervention for Challenging Behavior in Advanced Dementia: A Cluster Randomized Controlled Trial*. J Am Geriatr Soc, 2016. **64**(2): p. 261-9.
58. Lichtwarck, B., et al., *Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms: A Cluster Randomized Controlled Trial*. Am J Geriatr Psychiatry, 2018. **26**(1): p. 25-38.
59. Husebo, B.S., et al., *The Effect of a Multicomponent Intervention on Quality of Life in Residents of Nursing Homes: A Randomized Controlled Trial (COSMOS)*. J Am Med Dir Assoc, 2019.

60. Garcia-Gollarte, F., et al., *An educational intervention on drug use in nursing homes improves health outcomes resource utilization and reduces inappropriate drug prescription.* J Am Med Dir Assoc, 2014. **15**(12): p. 885-91.
61. Pitkala, K.H., et al., *Education to reduce potentially harmful medication use among residents of assisted living facilities: a randomized controlled trial.* J Am Med Dir Assoc, 2014. **15**(12): p. 892-8.
62. Westbury, J., et al., *An effective approach to decrease antipsychotic and benzodiazepine use in nursing homes: the RedUSe project.* Int Psychogeriatr, 2010. **22**(1): p. 26-36.
63. Crotty, M., et al., *An outreach geriatric medication advisory service in residential aged care: a randomised controlled trial of case conferencing.* Age Ageing, 2004. **33**(6): p. 612-7.
64. Tjia, J., et al., *Dissemination of Evidence-Based Antipsychotic Prescribing Guidelines to Nursing Homes: A Cluster Randomized Trial.* J Am Geriatr Soc, 2015. **63**(7): p. 1289-98.
65. Ray, W.A., et al., *Reducing antipsychotic drug prescribing for nursing home patients: a controlled trial of the effect of an educational visit.* Am J Public Health, 1987. **77**(11): p. 1448-50.
66. Massot Mesquida, M., et al., *Consensus and evidence-based medication review to optimize and potentially reduce psychotropic drug prescription in institutionalized dementia patients.* BMC Geriatr, 2019. **19**(1): p. 7.
67. Dahl, L.J., et al., *Quality improvement in long term care: the psychotropic assessment tool (PAT).* J Am Med Dir Assoc, 2008. **9**(9): p. 676-83.
68. Ray, W.A., et al., *Reducing antipsychotic drug use in nursing homes. A controlled trial of provider education.* Arch Intern Med, 1993. **153**(6): p. 713-21.
69. Westbury, J.L., et al., *RedUSe: reducing antipsychotic and benzodiazepine prescribing in residential aged care facilities.* Med J Aust, 2018. **208**(9): p. 398-403.
70. Carnahan, R.M., et al., *Impact of programs to reduce antipsychotic and anticholinergic use in nursing homes.* Alzheimers Dement (N Y), 2017. **3**(4): p. 553-561.
71. Tjia, J., et al., *Association of a Communication Training Program With Use of Antipsychotics in Nursing Homes.* JAMA Intern Med, 2017. **177**(6): p. 846-853.
72. Vida, S., et al., *A long-term care center interdisciplinary education program for antipsychotic use in dementia: program update five years later.* Int Psychogeriatr, 2012. **24**(4): p. 599-605.
73. Monette, J., et al., *Effect of an interdisciplinary educational program on antipsychotic prescribing among nursing home residents with dementia.* Int J Geriatr Psychiatry, 2008. **23**(6): p. 574-9.
74. ter Meulen, B.S., M.; Molewijk, B., *Bespreek ethische dilemma's in moreel beraad.* Medisch Contact, 2016. **04**: p. 34-37.
75. Janssens, J., et al., *Medical and moral considerations regarding complex medical decisions in older patients with multimorbidity: a compact deliberation framework.* BMC Geriatr, 2018. **18**(1): p. 25.
76. Alzheimer Europe, *Ethical dilemmas faced by health and social care professionals providing dementia care in care homes and hospital settings*. 2015.

Verzorgende: Door dat gebruik van die cipramil [...] zit ze niet zo in dat verdriet. Ze vraagt nog wel: 'Kan ik naar huis?' Maar het is niet meer die huilbuien [...]. Als je [...] haar op die manier toch nog wat kunt laten lachen, nog kunt laten genieten, dan denk ik: oké, dat is hartstikke goed dat ze dat krijgt.

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Chapter 9

Summary

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Summary

Almost all nursing home residents with dementia develop neuropsychiatric symptoms during their stay. Those symptoms are frequently treated with psychotropic drugs such as anti-psychotics, antidepressants, anxiolytics and hypnotics, despite limited evidence for effect. Moreover, they can cause serious side effects.

The objective of this thesis is to find new angles on improving the psychopharmacological treatment of neuropsychiatric symptoms in patients with dementia. It aims to explore which factors are involved in the prescription of psychotropic drugs, and to reduce prescription by means of structured and repeated multidisciplinary medication reviews.

Chapter 2 describes the design of the first part of our study named PROPER (PRescription Optimization of Psychotropic drugs in Elderly nuRsing home patients with dementia). This investigation used mixed methods, i.e. a qualitative and a quantitative study. It aimed to identify factors that are associated with the prescription of psychotropic drugs, and to determine the current prescription rates.

Chapter 3 presents the results of the qualitative study. We interviewed fifteen physicians and fourteen nurses individually. Every interview was audio-recorded, transcribed, and coded. Coding was conducted and refined until no new information could be added. We developed a conceptual framework consisting of four themes that enhance or limit prescription: *mindset* (beliefs and attitudes of the stakeholders), *knowledge and experience* (what stakeholders know and are capable of), *communication and cooperation* (interactions leading to teamwork), and *external possibilities/limitations* (preconditions on institutional and national level). These themes not only regarded psychotropic drugs, but also the underlying neuropsychiatric symptoms. Further, the discontinuation of previous prescriptions appeared to merit attention.

Chapter 4 reports about the results of the quantitative study. This had a cross-sectional, observational design and aimed to explore associations with the so far understudied psychosocial non-patient-related factors, and to determine prevalence rates. Participants were 559 nursing home patients with dementia, 25 physicians, and 112 nurses from 12 nursing homes throughout the Netherlands. We included possibly relevant factors, based on their fit in the four themes from the qualitative study. Multivariate multilevel regression analyses revealed that from 26 factors, only two showed a statistically significant association: antipsychotic prescription was less likely with higher availability of physicians and the odds for antidepressant prescription was higher when nurses were more satisfied with their patient contact. The non-patient-related factors had a very limited contribution to the explained variance. We found the following prevalence rates: 56% of patients were prescribed any psychotropic drug, 25% antipsychotics, 29% antidepressants, 15% anxiolytics, and 13% hypnotics. There were large differences between the different participating units.

Chapter 5 presents a meta-epidemiological study that investigates the impact of methodological decisions in trials on the pooled effect of antipsychotics. We postulated that efficacy of antipsychotics for agitation and psychosis in dementia is best estimated in trials that actually included patients with these symptoms and that used symptom-specific assessment scales. We investigated whether clinically broader definitions affected the pooled effect. A comprehensive literature search yielded thirty trials that met the inclusion criteria. These were categorized based on patient population (agitation, psychosis, any neuropsychiatric symptom) and assessment scale (agitation, psychosis, generic). For each combination of population and scale, we calculated standardized mean differences with 95% confidence intervals. We found that conventional antipsychotics might have a small effect in agitated patients on agitation scales, and in psychotic patients on psychosis scales. There was no effect on generic scales. Efficacy of atypical antipsychotics was not established in agitated patients on agitation scales, nor in psychotic patients on psychosis scales, but was small in patients with any neuropsychiatric symptoms on agitation scales. We concluded that the effect of antipsychotics for agitation and psychosis in dementia is biased when it is based upon trials that included patients not necessarily having these target symptoms, or upon results measured with generic scales. These findings illustrate that proper prescription is subject to progressing insights.

Chapter 6 presents the design of the second part of the PROPER study. This part had a cluster randomized controlled design with two parallel groups (intervention versus usual care) and assessments at 0, 6, 12, and 18 months. The PROPER intervention consisted of structured and repeated multidisciplinary medication reviews, supported by education and continuous evaluation. The intervention was conducted by pharmacists, physicians, and nurses and consisted of three components: 1) preparation and education, 2) conduct, and 3) evaluation/guidance.

Chapter 7 reports about the effect of the PROPER intervention on the prevalence of psychotropic drug prescriptions, and on the occurrence of the underlying neuropsychiatric symptoms. The trial was conducted among 380 patients with dementia from 13 long term care organizations in the Netherlands. The prescription of any type of psychotropic drugs increased in the intervention group, and decreased in the control group. The occurrence of neuropsychiatric symptoms remained stable. These negative results may be explained by the fact that the PROPER intervention was too narrow given the broad range of factors that were found to contribute to prescription in the qualitative study.

Chapter 8 aims to put proper prescription in perspective. This thesis shows that there are many closely related and interactive factors involved in the psychopharmacological treatment of neuropsychiatric symptoms. Prescription is therefore complex and should be regarded and judged in its context. For improving prescription, it may be necessary to address the context as comprehensively as possible. Of all factors, those relating to *communication* may be the most accessible and susceptible to change. Communication may therefore be an important vehicle to improve prescribing. The chapter ends with implications for researchers, health care professionals, policy makers, and nursing home management.

Publiekssamenvatting

Op dit moment zijn er in Nederland naar schatting 270.000 mensen met dementie. Hiervan wonen er 70.000 in een zorginstelling. Bij dementie wordt vaak gedacht aan geheugenproblemen. Maar mensen met dementie krijgen ook vaak veranderingen in gedrag. Bijna alle verpleeghuisbewoners met dementie ontwikkelen probleemgedrag. Onder dat begrip vallen bijvoorbeeld agressie en agitatie, maar ook psychose en depressieve symptomen. Vaak wordt dat gedrag behandeld met rustgevende medicatie, de zogenaamde psychofarmaca. Er zijn verschillende groepen psychofarmaca, zoals antipsychotica, antidepressiva, anxiolytica en hypnotica.

Uit onderzoek blijkt echter, dat die psychofarmaca maar heel weinig effect hebben op probleemgedrag. Daarbij weten we dat ze wel bijwerkingen kunnen geven zoals spierstijfheid en sufheid. Ze kunnen ook een verhoogd risico geven op vallen, beroerte en mogelijk zelfs vroegtijdig overlijden. En toch wordt er vaak voor behandeling met psychofarmaca gekozen.

In dit proefschrift proberen we te achterhalen waarom er dan toch voor behandeling met psychofarmaca wordt gekozen, en of gestructureerde en herhaalde medicatiebeoordelingen helpen om dit voorschrijven te verminderen. Dit onderzoek, de PROPER studie, gaf ook de gelegenheid te kijken hoeveel psychofarmaca er worden voorgeschreven. Daarna zijn alle bevindingen in perspectief geplaatst.

Om te onderzoeken waarom er voor psychofarmaca wordt gekozen, hebben we artsen en verzorgenden geïnterviewd. Dit was een zogenaamd kwalitatief onderzoek. Alle interviews werden opgenomen, alles wat gezegd werd is letterlijk uitgeschreven en we hebben deze teksten geanalyseerd. We vonden vier groepen van factoren die een rol spelen. En die vier hebben niet alleen betrekking op psychofarmaca, maar ook op probleemgedrag. Dit hebben we samengevat in een model.

De eerste groep factoren gaat over *houding* en belangen. Er zijn veel mensen betrokken bij het proces van voorschrijven. Uiteraard de bewoner zelf, maar ook de familie, verzorgenden, medebewoners, de arts en de psycholoog. En die mensen hebben allemaal een idee rondom probleemgedrag (het mag er zijn, of niet) en rondom psychofarmaca (ze zijn slecht, of ze kunnen een oplossing bieden). De tweede groep gaat over de *kennis en kunde* van die belanghebbenden. Of ze weten wat te doen bij probleemgedrag, of hoe ze het kunnen voorkomen. Of ze weten wat de bijwerkingen zijn van psychofarmaca en ervaring hebben met voorschrijven. De derde groep gaat over *communicatie en samenwerking*. Praten ze met elkaar? Over wat ze vinden, wat ze weten, wat ze kunnen, waar ze tegenaan lopen? En de vierde gaat over de *mogelijkheden en beperkingen*: is er voldoende tijd voor de zorg die het probleemgedrag vraagt? Wat is op dit moment de publieke opinie over psychofarmaca? De factoren in die vier groepen spelen allemaal een rol als het gaat om het voorschrijven van psychofarmaca.

We hebben ook cijfermatig gekeken of deze factoren een verband hebben met voorschrijven. Dat deden we via een vragenlijstonderzoek. Hieraan deden 559 verpleeghuisbewoners, 25 artsen en 112 verzorgenden van 12 Nederlandse zorginstellingen mee. Van de 26 factoren bleken er echter maar twee een statistisch significant verband te laten zien. Beide gingen over communicatie. Dat is niet meer dan wat je op basis van toeval verwacht. Maar dat we onze bevindingen niet konden kwantificeren betekent niet dat het bovengenoemde model niet klopt. We vermoeden dat de meetmethode niet geschikt was om de factoren te meten die we vonden in de interviews. Het vragenlijstonderzoek gaf wel inzicht in de voorschrijfcijfers: 56% van de verpleeghuisbewoners kreeg een of meer psychofarmaca, 25% kreeg een antipsychoticum, 29% een antidepressivum, 15% een anxiolyticum en 13% een hypnoticum. Er waren grote verschillen in deze percentages tussen de deelnemende afdelingen. Dat betekent dat er waarschijnlijk verbetering mogelijk is, zeker op afdelingen waar de percentages hoog zijn.

Uit werk wat we gedaan hebben voor een herziening van de richtlijn probleemgedrag van de beroepsvereniging voor specialisten ouderengeneeskunde, Verenso, kwam ook een interessant inzicht naar voren. Voor die richtlijn hebben we uitgebreid gezocht naar alle onderzoeken met antipsychotica die effect hadden gemeten op agitatie en psychose bij mensen met dementie. Om vervolgens een gemiddelde te berekenen van het effect. Tot dan toe werden daarbij alle onderzoeken bij mensen met dementie meegenomen. Maar voor de nieuwe richtlijn was besloten, dat we alleen onderzoeken zouden meenemen bij mensen met dementie, die ook daadwerkelijk agitatie of psychose hadden. En dat we alleen de resultaten op die specifieke symptomen relevant vonden. Door op deze manier te kijken, leek het effect van de langer geleden ontwikkelde 'conventionele' antipsychotica op agitatie en psychose tot dan toe te zijn onderschat, terwijl het effect van de nieuwere, 'atypische' antipsychotica op agitatie juist leek te zijn overschat. Dit kan worden gezien als een voorbeeld. Kennelijk zijn de ideeën over een juiste wijze van voorschrijven ook gevoelig voor voortschrijdend inzicht.

We hebben als onderdeel van de PROPER studie daarnaast een zogenaamd gerandomiseerd, gecontroleerd onderzoek uitgevoerd. Daarmee wilden we onderzoeken of medicatiebeoordelingen helpen om minder psychofarmaca voor te schrijven. Vooraf werd er een training gegeven over het doen van medicatiebeoordelingen. Deze werden vervolgens halfjaarlijks uitgevoerd door apothekers, artsen en verzorgenden. Het onderzoek duurde anderhalf jaar, waarbij elk half jaar het effect werd gemeten. Er deden 380 bewoners van 13 zorginstellingen aan mee. Op basis van toeval voerde de ene helft van de instellingen de medicatiebeoordelingen uit, terwijl de andere helft doorging met de gebruikelijke zorg (de controlegroep). Na afloop bleken er echter juist meer psychofarmaca te zijn voorgeschreven op de afdelingen die meededen aan de medicatiebeoordelingen. Misschien komt dat, doordat er veel verloop is geweest in de bewoners. Het effect van veranderingen in de bewoners kan wel eens groter zijn geweest dan het effect van de medicatiebeoordelingen. Mogelijk speelde ook een rol dat veel controleafdelingen al op hun manier medicatiebeoordelingen deden. Maar wij denken dat de interventie ook te beperkt was. Deze was vooral gericht op het kritisch bekijken van medicatie, terwijl we

uit de interviews kunnen concluderen dat er veel meer factoren bijdragen aan het voorschrijven van psychofarmaca.

Tot slot zijn bovenstaande bevindingen over de behandeling van probleemgedrag met psychofarmaca in perspectief geplaatst. Dit proefschrift laat zien dat het voorschrijven heel complex is en altijd in de context moet worden beschouwd. Als we voorschrijven willen aanpakken, is het waarschijnlijk nodig die gehele context te adresseren. Tot nu toe is er vooral een focus op *kennis en kunde*, maar op basis van ons model verdienen *communicatie en samenwerking* zeker zoveel aandacht. Door beter met elkaar te af te stemmen is er mogelijk veel te winnen in het beter voorschrijven van psychofarmaca bij deze kwetsbare groep van verpleeghuisbewoners met dementie.

Research data management statement

The research data presented in this thesis were collected and stored according to the regulations at the time.

For the PROPER study (chapters 3, 4, and 7), we used audio recordings, web-based and hardcopy questionnaires. Electronic data were stored on the Radboud university medical center server. Anonymous data were archived at H:\OZ-Dementie\PROPER, the key at H:\OZ-Sleutelbestanden\PROPER. Hardcopy data including questionnaires, data cleaning documentation and the key are stored until November 2030 in the Radboud university medical center archives. Data are accessible from the associated senior staff members upon reasonable request.

For chapter 5, we used public trial results and some data that were provided by the authors of trials. Data that were retrieved and used for the analyses are accessible from the associated corresponding author upon reasonable request.

Portfolio

Congressen en symposia

- International Psychogeriatric Association Congress, 6 t/m 9 september 2011, Den Haag; posterpresentatie
- CCZ-EBP Minisymposium, 17 december 2013, Nijmegen; presentatie
- Universitair Kennisnetwerk Ouderenzorg Nijmegen Symposium, 15 april 2014, Nijmegen; presentatie
- Gerion Symposium, 5 september 2014, Amsterdam; presentatie
- Verenso Najaarscongres, 27 november 2014, Apeldoorn; presentatie
- Congress of the European Union Geriatric Medicine Society, 17 t/m 19 september 2014, Rotterdam; posterpresentatie
- International Psychogeriatric Association Congress, 13 t/m 16 oktober 2015, Berlijn; posterpresentatie
- Verenso Najaarscongres, 30 november 2017, Ede; flits- en posterpresentatie
- Congres Zoek het uit! van Vilans en het Ministerie van Volksgezondheid, Welzijn en Sport, 31 januari 2019, Nieuwegein; workshop
- Universitair Kennisnetwerk Ouderenzorg Nijmegen Symposium, 9 april 2019, 's-Hertogenbosch; workshop
- Samenwerkende Academische Netwerken Ouderenzorg Wetenschapsdag, 6 juni 2019, Nijmegen; workshop

Cursussen

- NCEBP Introduction Course for PhD students, 26 t/m 29 maart 2012, Nijmegen
- Write an article and get it published, 20 september 2012, Utrecht
- BROK certificaat 12 oktober 2012 en herregistratie 6 september 2016, Nijmegen
- Introduction to Multilevel Analysis Summer School, 8 t/m 11 juli 2013, Utrecht
- Qualitative Research Methods in Health Care (Introduction), 14 en 21 november 2013, Nijmegen
- Onderzoeker in de klas, april t/m mei 2014, Nijmegen
- The Art of Presenting Science; mei en juni 2014, Nijmegen

Dankwoord

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Mijn lieve vriendinnen en vrienden, van wie speciaal Kirsten, Claudia, Lotte en Marjoleine: dank voor jullie betrokkenheid en het delen van alle andere dingen die zo waardevol zijn in het leven.

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Curriculum Vitae

Claudia Smeets werd geboren op 25 januari 1976 in Weert. Ze groeide op in Budel als middelste in een gezin van drie kinderen. Na het behalen van haar gymnasiumdiploma in 1994, vertrok ze naar Antwerpen om daar Geneeskunde te gaan studeren. In 1997 maakte ze de overstap naar Medische Biologie in Amsterdam. Afstudeerprojecten bij het Nederlands Instituut voor Hersenonderzoek en de Psychiatrische Universitätsklinik in Basel waren haar eerste onderzoekservaringen bij mensen met dementie in het verpleeghuis. In 2001 behaalde ze haar doctoraal, daarna ging ze werken in het bedrijfsleven.

Claudia startte bij Kendle in Utrecht, waar ze zich bezighield met operationele aspecten van klinisch onderzoek. Omdat ze de wetenschap ging missen, volgde ze in haar vrije tijd de postdoctorale opleiding tot epidemioloog. Toen ze in 2005 een baan kreeg aangeboden waarbij ze operationele en wetenschappelijke taken van klinisch onderzoek kon combineren, ging ze werken bij Numico (later Danone) Research in Wageningen. Ze had daar aanvankelijk een functie als onderzoeker, later als team leader. Ze werkte mee aan nationale en internationale studies met voeding voor patiënten met de ziekte van Alzheimer en voor baby's.

Gegrepen door het onderwerp, startte ze in 2011 met haar promotietraject aan het Radboudumc. In 2016 trad ze in dienst bij het Universitair Medisch Centrum Groningen om daar literatuuronderzoek, meta-analyses en GRADE beoordelingen te doen voor de herziening van de Verenso Richtlijn Probleemgedrag bij mensen met dementie. In 2017 werd haar voor twee jaar subsidie toegekend om vanuit het Radboudumc de bevindingen uit het promotieonderzoek te implementeren. Ze ontwikkelde daarvoor het stappenplan 'Multidisciplinair samen werken aan passend gebruik van antipsychotica', wat inmiddels bij vier instellingen begeleid en bij twee instellingen zelfstandig wordt doorlopen.

Claudia woont met haar man Gerbrand en hun dochters Wiepke (2011) en Eef (2013) in Molenhoek.

Almost all nursing home patients with dementia experience neuropsychiatric symptoms during their stay. These symptoms are frequently treated with psychotropic drugs, despite limited evidence for effect and risks of considerable side effects.

This thesis shows that many, interacting, factors contribute to prescribing psychotropic drugs. It also shows that the PROPER intervention, consisting of structured and biannual multidisciplinary medication reviews, was not effective in reducing prescription. The findings illustrate that prescription is complex and should be regarded within its context. Communication may be an interesting tool to improve the psychopharmacological treatment of neuropsychiatric symptoms.