Can the PROPER intervention reduce psychotropic drug prescription in nursing home residents with dementia? Results of a cluster-randomized controlled trial

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ABSTRACT

Objectives: To evaluate the effect of the PROPER intervention in nursing home residents 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: Thirty-one dementia special care units within 13 long-term care organizations in the Netherlands.

Participants: Three hundred eighty nursing home residents 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 percentage points per 6 months ($p = 0.01$). Effects for the individual drug groups were minor (differences of 1.6 percentage points and below per 6 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.

The study has been registered in The Netherlands Trial Register (NTR3569).

Key words: psychopharmacology, neuropsychiatric symptoms, behavioral and psychological symptoms of dementia, dementia, nursing homes

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Introduction

Neuropsychiatric symptoms are highly prevalent in people with dementia, especially among those who live in long-term care organizations

(Selbaek *et al.*, 2013). These symptoms are frequently treated with psychotropic drugs, despite limited efficacy and enlarged risks of side effects, particularly for antipsychotics (Ballard and Waite, 2006). 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, and their implementation varied (Avorn *et al.*, 1992; Ballard *et al.*, 2016; Crotty *et al.*, 2004; Fossey *et al.*, 2006; Ray *et al.*, 1987; Tjia *et al.*, 2015; Westbury *et al.*, 2010).

In the Netherlands, nursing home care for people with dementia is organized differently than in most countries. Those people 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, and by nurses (Koopmans *et al.*, 2017). Nursing education is divided into five levels, which we consider comparable with nursing assistant (level 1 and 2), certified nursing assistant (level 3), and registered nurse (level 4 and 5). When prescribing psychotropic drugs, these physicians can make use of the Guideline for problem behavior of the Dutch body representing elderly care physicians (Verenso) (Smalbrugge *et al.*, 2008). Despite differences in care, psychotropic drugs are prescribed with similar prevalence rates compared to other Western European countries (Janus *et al.*, 2016).

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 residents' 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 (Nederlands Huisartsen Genootschap, 2012; Smalbrugge *et al.*, 2008).

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 (van der Spek *et al.*, 2018a). The current study is conducted at the resident level. It aims to evaluate the effect of the PROPER intervention in nursing home residents 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 (Smeets *et al.*, 2013). We used a cluster-randomized controlled design with two parallel groups (intervention versus usual care) and assessments at 0, 6, 12, and 18 months.

Participants

All residents living in the participating DSCUs were eligible for inclusion if they had a chart diagnosis of dementia. Participants who dropped out were replaced by residents 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 (IVM) (Instituut Verantwoord Medicijngebruik). It prescribes adherence to the Guideline for problem behavior of the Dutch Association of Elderly Care Physicians, 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]) (Gallagher *et al.*, 2008; Nederlands Huisartsen Genootschap, 2012; Smalbrugge *et al.*, 2008).

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, that is, to respectively obtain medical information, pharmacological information,

and knowledge on the resident'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 resident'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 (Nordic Council on Medicines, 1990). 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, since the actual use could not reliably be collected.

Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory – Questionnaire (NPI-Q) and the Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield *et al.*, 1989; Kaufer *et al.*, 2000). 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" (Zuidema *et al.*, 2011). The CMAI includes 29 items on physical aggression, physically nonaggressive 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) (Reisberg *et al.*, 1982).

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 residents' care. The web-based GDS questionnaires were completed by the residents' physicians. Participants were not directly involved in the study. Assessments were conducted at baseline, and after 6, 12, and 18 months.

Cluster 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. There was no blinding in this study. Allocation was computer-generated and conducted by a statistician.

DSCU and participant selection

In line with the sample size calculation of the primary outcome, we included the 12 organizations that had participated in the previously conducted PROPER I study, supplemented with an additional organization to account for potential dropout of an organization (Smeets *et al.*, 2013). From each organization, we randomly selected two DSCUs, and from each DSCU 15 residents. If a DSCU had less than 15 residents, we included 1 or more additional DSCUs in order to reach at least 30 residents 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. Although the use of psychotropic drugs was binary, it was our focus to diminish the DSCU averages of percentage prescriptions (i.e. a population-averages as opposed to subject-specific estimates). Therefore, we aimed at interpretation of differences in percentage points. Subsequently, we used linear mixed models with identity links 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, and we expected the averages to be normally distributed. We assessed model fit by checking if the

residuals were normally distributed, and by checking the residuals of the mixed models and the observed-versus-predicted-value plots. All analyses were conducted intention-to-treat with IBM SPSS Statistics for Windows, Version 22.0 (Armonk, 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 *et al.*, 2019). 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 (World Medical Association, 2013). The representatives of the residents on the participating DSCUs were informed about the study in writing and given the explicit opportunity to refrain from the resident'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 13 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 residents (at all assessments), overall range 4 to 19. There were 21 physicians involved in the intervention group, with turnover in all organizations. In the control group, there were 14 other physicians involved, with turnover in half of the organizations.

Participant flow

A total of 380 residents were included. In the intervention group, 170 participants dropped out (143 due to death, transfer to another unit, no diagnosis of dementia was found in charts by the researchers, or withdrawal during the study and 27 due to the withdrawal of the organization) and were replaced by 120 new residents versus 90 dropouts and 83 replacements in the control group. A total of 323 residents completed the final assessment, 186 of whom participated from baseline onward (92 in intervention and 94 in the control group). Details are shown in Figure 1.

Baseline characteristics

Table 1 presents the baseline characteristics. In the intervention group, the proportion of participants 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.

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 6 months with 95% confidence intervals.

PSYCHOTROPIC DRUG PRESCRIPTION
The observed prevalence of any psychotropic drug prescription increased by 5 percentage points (SD 22) from baseline to the final assessment in the intervention group and decreased by 8 percentage points (SD 13) in the control group. The model estimated difference between the slopes for use of any psychotropic drug increased by 3.9 percentage points every 6 months ($p = 0.01$). Prescription of antipsychotics in the intervention group was observed to decrease by 5 percentage points (SD 20) from baseline to 12 months, but then to increase again by 4 percentage points (SD 6). In the control group, the antipsychotic prescription consistently was observed to decrease by a total of 5 percentage points (SD 11) from baseline to 18 months. Antidepressant or hypnotic prescriptions did not change in the intervention group and was observed to decrease in the control group by 2 (SD 15) and 3 percentage points (SD 10), respectively. The prescription of anxiolytics was observed to increase by 4 percentage
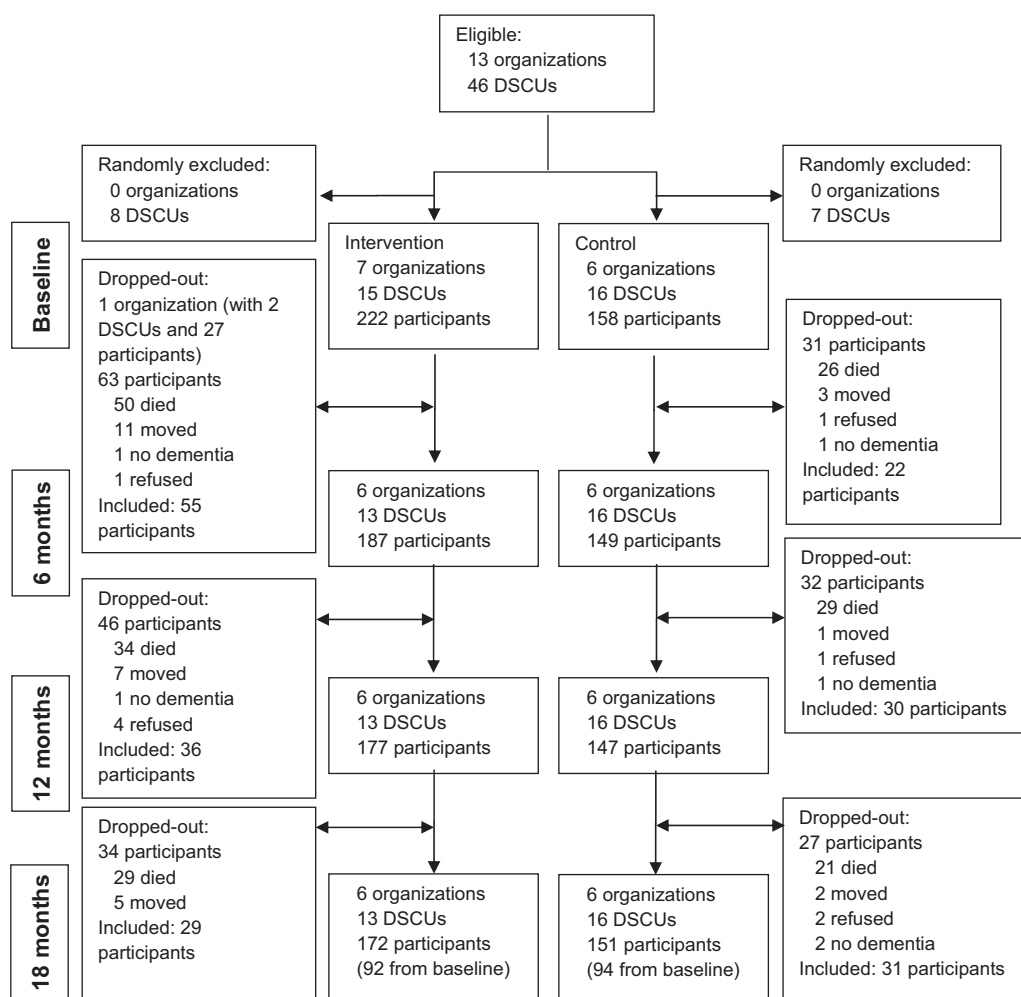
Figure 1. Flow chart.

points (SD 12) in the intervention group and to decrease by 1 percentage point (SD 9) in the control group. Slope differences of the individual drug groups as estimated by the model were small (1.6 percentage points 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 was observed to increase 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, but not statistically significant estimated slope difference of 0.6 every 6 months.

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.

Discussion

We found that the PROPER intervention did not reduce the prescription of antipsychotics, antidepressants, hypnotics, nor anxiolytics for neuropsychiatric symptoms in nursing home residents with dementia. The prescription of psychotropic drugs increased in the intervention group, whereas it decreased in the control group. The occurrence of

Table 1. Baseline characteristics

CHARACTERISTIC	INTERVENTION	CONTROL
Number of participants	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.

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 dropout rate in the intervention group was almost twice as high as in the control group. Although this was partly due to dropout of one organization, there was still a substantially higher dropout 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 residents is likely to have missed the effect of the first medication review round, whereas the effect on prescriptions for participants 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 (Smeets *et al.*, 2017). However, this would have raised the issue of how to operationalize this correction. The total NPI score for instance includes

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 pp	0.01
	control	50% [17%]	49% [21%]	44% [22%]	42% [16%]	[0.9–6.9]	
Antipsychotics	intervention	27% [22%]	24% [17%]	22% [16%]	26% [15%]	1.3 pp	0.33
	control	20% [14%]	19% [15%]	18% [18%]	15% [11%]	[−1.3–4.0]	
Antidepressants	intervention	27% [18%]	29% [20%]	29% [16%]	27% [8%]	0.2 pp	0.90
	control	24% [13%]	25% [17%]	26% [17%]	22% [16%]	[−2.7–3.1]	
Hypnotics	intervention	14% [13%]	17% [11%]	14% [12%]	14% [13%]	1.1 pp	0.37
	control	12% [13%]	14% [13%]	11% [14%]	9% [11%]	[−1.2–3.4]	
Anxiolytics	intervention	14% [10%]	15% [10%]	16% [11%]	18% [9%]	1.6 pp	0.13
	control	15% [11%]	19% [13%]	15% [11%]	14% [12%]	[−0.5–3.6]	
NPI total severity	intervention	6.4 [2.9]	5.4 [3.8]	6.5 [3.8]	6.4 [3.0]	0.3	0.24
	control	6.3 [2.1]	5.9 [2.3]	5.7 [2.5]	5.4 [2.4]	[−0.2–0.8]	
NPI total distress	intervention	5.0 [3.8]	4.0 [3.9]	6.1 [5.7]	5.0 [3.8]	0.1	0.69
	control	5.2 [3.3]	5.1 [2.9]	5.6 [3.2]	4.6 [3.3]	[−0.5–0.8]	
CMAI total	intervention	44.0 [6.3]	44.1 [8.9]	46.4 [9.9]	46.6 [7.7]	0.6	0.45
	control	44.1 [5.7]	43.5 [7.2]	44.0 [7.2]	44.6 [10.4]	[−0.9–2.1]	

*Any: any antipsychotic, antidepressant, hypnotic, and/or anxiolytic.
Abbreviations: SD: standard deviation; CI: confidence interval; pp: percentage point; 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

VARIABLE	RESULTS WITHOUT ORGANIZATION NOT ADHERING TO INTERVENTION PROCEDURES		RESULTS WITHOUT ORGANIZATIONS ALREADY CONDUCTING MEDICATION REVIEWS	
	DIFFERENCE IN SLOPES PER 6 MONTHS [95% CI]	p	DIFFERENCE IN SLOPES PER 6 MONTHS [95% CI]	p
Any psychotropic drug*	3.6 pp [0.4–6.8]	0.03	4.7 pp [0.8–8.7]	0.02
Antipsychotics	1.5 pp [−1.4–4.3]	0.31	1.2 pp [−2.6–5.0]	0.53
Antidepressants	0.1 pp [−3.0–3.2]	0.95	2.4 pp [−1.1–6.0]	0.17
Hypnotics	0.2 pp [−2.2–2.6]	0.88	1.9 pp [−1.4–5.2]	0.26
Anxiolytics	1.4 pp [−0.7–3.6]	0.19	0.4 pp [−2.3–3.2]	0.77

*Any: any antipsychotic, antidepressant, hypnotic, and/or anxiolytic.
Abbreviations: CI: confidence interval; pp: percentage point.

a variety of symptoms (Smeets *et al.*, 2018). 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 (van der Spek *et al.*, 2018a).

This implied that there was an improvement in the evaluation (i.e. the use of the drug was evaluated with a specified time frame 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) (van der Spek *et al.*, 2015). 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 (Smeets *et al.*, 2014). These themes do not only refer to psychotropic drugs, but also to the underlying cause for prescription, that is, 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 comprise 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 (Ballard *et al.*, 2009; Ballard *et al.*, 2016; Tjia *et al.*, 2017), and interventions that aimed for early detection and treatment of neuropsychiatric symptoms appear more successful in the reduction of psychotropic drug use (Rapp *et al.*, 2013; Zwijsen *et al.*, 2014). 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 (Birkenhager-Gillesse *et al.*, 2018).

Second, the study is conducted in a time frame in which awareness of the prescription of psychotropic drugs is already high (Smalbrugge *et al.*, 2008). 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, that is, the Hawthorne effect (Sedgwick and Greenwood, 2015).

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 residents per DSCU, which means that prescription changes of individual participants 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 residents 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 (Bolzern *et al.*, 2018). Both the stage and type of dementia are expected to be correlated with the extent of neuropsychiatric symptoms (Caputo *et al.*, 2008). 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, the turnover of physicians was higher in the intervention group than in the control group. As staff turnover may affect prescription, this may have influenced the results (Smeets *et al.*, 2014). Fourth, one intervention organization did not fully adhere to the intervention procedures. However, the sensitivity analysis excluding this organization did not show different results.

Recent publications in International Psychogeriatrics illustrate the complexity to improve prescription. Whereas local initiatives such as CHROME can be very successful and prescription rates may have declined over time like in Norway (Muniz *et al.*, 2019; Selbaek *et al.*, 2018), prescription remained high in other countries like Australia and the Netherlands (McMaster *et al.*, 2018; van der Spek *et al.*, 2018b). Aside from prevalence rates, appropriateness of prescription has become an increasingly important measure (Brimelow *et al.*, 2019; Harrison *et al.*, 2020; van der Spek *et al.*, 2018b). Further, it appears that improving prescription involves more than focusing on medication. An international consensus panel stipulated to search for underlying causes of neuropsychiatric symptoms and to apply non-pharmacological interventions including staff training and environmental changes, prior to prescribing psychotropic drugs (Kales *et al.*, 2019).

Moreover, interventions that aim to improve prescription should have a broad approach: they should target not only psychotropic drugs but also skills of care staff (Ballard and Corbett, 2020). Further, successful implementation of interventions to improve prescription requires a few preconditions on nursing home level, such as sufficient resources, strong communication, leadership, and management support (Gerritsen *et al.*, 2019; Groot Kormelinck *et al.*, 2020).

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.

Conflict of interest

None.

Author contributions

Smeets: acquisition of subjects and data, statistical analyses, manuscript writing. Smalbrugge and Koopmans: obtaining funding, study design. Nelissen-Vrancken: advice and management of the intervention. Van der Spek: acquisition of subjects and data. Teerenstra: statistical consultant. Gerritsen: obtaining funding, study design, project management. Zuidema: obtaining funding, study design, statistical advice. All authors participated in formulation of the research questions, result interpretation, manuscript revision and approved the final version.

Acknowledgments

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