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

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Abstract

Objective: We studied the efficacy of biannual structured medication reviews to improve the appropriateness of psychotropic drug (PD) prescriptions for neuropsychiatric symptoms (NPS) in nursing home patients with dementia.
Study Design and Setting: In this randomised controlled trial, the intervention encompassed a structured multidisciplinary medication review by physician, pharmacist and nurse. During this 18-month study, the patient's medical files were assessed every 6 months. The primary outcome was the appropriateness of PD prescriptions defined by the Appropriate Psychotropic drug use In Dementia (APID) index sum score, lower scores indicating more appropriate use.
Results: At baseline, 380 patients were included, of which 222 were randomised to the intervention group. Compared to the control group, the APID index sum score in the intervention group improved significantly for all PD prescriptions (−5.28, $P = 0.005$).
Conclusion: We advise the implementation of a structured, repeated medication review with the essential roles of pharmacist, physician and nurse, into daily practice. This work was supported and funded by the Netherlands Organisation for Health Research and Development (ZonMw). Netherlands Trial Register (NTR3569).

Keywords: *nursing homes, long-term care, potentially inappropriate prescribing, behavioural and psychological symptoms of dementia, older people*

Introduction

Many nursing home residents with dementia have neuropsychiatric symptoms which are frequently treated with psychotropic drugs, e.g. antipsychotics, antidepressants, anxiolytics and hypnotics [1, 2]. However, there is substantial evidence for the existence of risks, side effects and long-term inefficacy of psychotropic drugs [3, 4], which is why the guidelines recommend the restricted and short-term use [5]. Nevertheless, there is some literature available reporting that psychotropic

drugs are being used for excessively long periods [6–8], simultaneously [1], and without a proper indication [9, 10]. These findings suggest inappropriate psychotropic drug prescriptions, thereby emphasising the need for optimisation strategies.

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

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

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

Methods

Trial design

The PROPER II study (PRescription Optimisation of Psychotropic drugs in Elderly nuRsing home patients with dementia) investigated the effects of a newly developed medication review intervention in a multi-centre, cluster randomised controlled pragmatic trial using parallel groups [20]. The intervention group performed a structured, repeated (psychotropic) drug review, and the control group continued care as usual [20]. The study was conducted for 18 months, with four biannual assessments.

Sample size

Allowing for a cluster drop-out of 10%, in total 23 clusters (i.e. dementia special care units), with 15 patients on average, would provide >80% power to detect an absolute difference of 20% in the appropriateness of psychotropic drug prescriptions, as detailed in the study design paper [20].

Recruitment and randomisation

The nursing homes recruited for PROPER II [20] were those already recruited for PROPER I, a cross-sectional mixed methods study that aimed to investigate (the appropriateness of) psychotropic drug prescriptions and its associations. For PROPER I, 27 long-term care organisations were contacted in order to include the necessary 13 nursing homes, located throughout the Netherlands. In the Netherlands, nursing homes are part of long-term care organisations and have dementia special care units that differ in size between 5 and 30 patients. Usually, individual patients have one registered nurse and an elderly care physician assigned that is primarily responsible for their care [21]. A random selection of the dementia special care units that participated in PROPER I [22] was included in PROPER II. On average, 30 patients per location were included, residing in two or more dementia special care units depending on the size of the units. Randomisation was blinded, i.e. computer-generated, and conducted on the level of nursing homes to prevent contamination bias within the nursing home. Seven nursing homes participated in the intervention and six continued care as usual.

Patient involvement and ethics

Patients were not directly involved in the study, information about psychotropic drug prescriptions were obtained from medical records. Physicians and nurses who were directly involved in the medical treatment and care for the patients collected data about the patients [20]. The inclusion criteria of PROPER II were (i) a chart diagnosis of dementia, (ii) not terminally ill and (iii) admitted for long stay. Patients who died or moved from the dementia special care unit were replaced by newly admitted patients on that units during the study. Representatives of all selected patients were approached in writing to inform them about the study and to give them the explicit opportunity to refrain from the participation of the patient in the study.

The local Medical Ethics Review Committee 'CMO Regio Arnhem-Nijmegen' judged/reviewed the study (number 2012/226) and pronounced that the study is carried out in accordance with the applicable rules in the Netherlands concerning the review of research ethics committees and informed consent.

PROPER II Intervention

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

The intervention consisted of three components:

Component 1: A preparation and education phase that included instruction about the practical and organisational aspects of the medication review and a training about the efficacy and side effects of psychotropic drugs, which were to be attended by physicians, pharmacists and nurses. The education was provided by the Dutch Institute for Rational Use of Medicine (IVM) and emphasised the adherence to the Guideline for problem behaviour of the Dutch Association of

Elderly Care Physicians and Social Geriatricians (Verenso) [5], the Multidisciplinary guideline Polypharmacy in the elder [23] (including the Systematic Tool to Reduce Inappropriate Prescribing (STRIP), the Screening Tool to Alert doctors to Right Treatment (START) and the Screening Tool of Older Person's potentially inappropriate Prescriptions (STOPP)[14]).

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

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

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

Assessments and outcomes

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

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

The primary outcome was the level of appropriateness of psychotropic drug use as defined by the Appropriate Psychotropic Drug use In Dementia index sum score. Secondary outcomes were the appropriateness of indication, evaluation and therapy duration, defined by the Appropriate Psychotropic drug use In Dementia index subscores on these domains [17]. The theoretical weighted score ranges for these domains of appropriateness are as follows: indication 0–18.8, evaluation 0–19.2 and therapy duration 0–12.2.

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

Baseline characteristics

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

Statistical analysis

Descriptive statistics were used to examine the baseline characteristics. When more than a 10% difference between the intervention- and control group was observed, an independent samples *t*-test was performed to test the effect of this parameter on the primary outcome (Appropriate Psychotropic drug use In Dementia index sum score). Adjacent small dementia special care units sharing staff and corridors that had few participating patients, i.e. ≤3 patients participating on each unit at one or more of the measurement points, were grouped prior to conduct of the statistical analyses. At baseline and after 6, 12 and 18 months, the mean index sum scores, the mean index subscores for indication, evaluation and therapy duration, including the standard deviations and 95% confidence intervals were calculated.

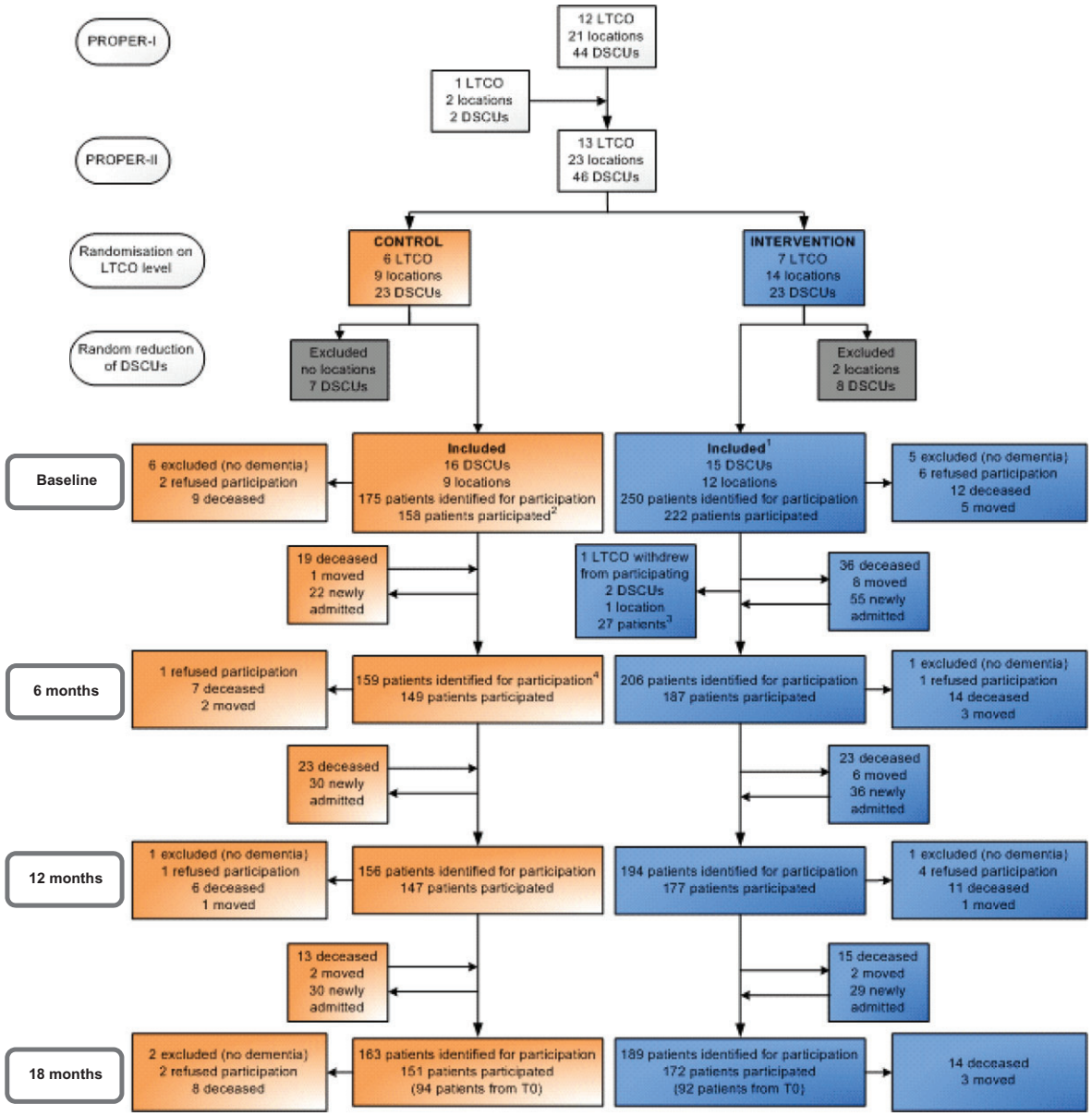
A linear mixed model for repeated measurements of the outcome averaged at dementia special care unit (cluster) levels was used with time and treatment (1 in the intervention group at 6, 12 and 18 months and 0 otherwise) as fixed effects (which is equivalent to a time x treatment interaction assuming no systematic difference between groups at baseline due to the randomisation) and dementia special care unit as random effect. Residuals of the mixed model were checked for trends indicating non-normal distribution. The effect in our trial was thus the average effect of the intervention versus control, averaged over month 6, 12 and 18 [24].

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

Results

Recruitment and flowchart

Eleven of the 27 long-term care organisations that were contacted decided not to take part because of (i) lack of



Study flowchart for the outcome analysis.

Notes

LTCO = Long term care organizations

DSCU = Dementia Special Care Unit

1. Two LTCOs overruled the randomised selection of DSCUs because the selected DSCUs were covered by the same physician and the workload would get too high.

2. A patient was considered a participant if the primary outcome (the appropriateness of psychotropic drug prescription) was collected/assessed.

3. After baseline, one LTCO randomised to the intervention group discontinued the study because of insufficient staffing of physicians.

4. One patient dropped out by mistake and was again included at 18 months.

Figure 1. Study flowchart for the outcome analysis.

time or insufficient staffing (physician or nurse) to carry out the project ($N = 5$); (ii) an ongoing reorganisation ($N = 3$); (iii) involvement in another (research) project ($N = 2$); and (iv) unit managers who were unwilling to participate ($N = 1$). The study was conducted from September 2012 to July 2014. The 12 long-term care organisations that completed the study were equally distributed over various rural and urban parts of the Netherlands.

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

Baseline characteristics

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

Outcomes measures

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

Table 1. Baseline characteristics

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

Outcomes specified per psychotropic drug group

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

Discussion

Main findings

This innovative study demonstrated that the appropriateness of psychotropic drug prescriptions for neuropsychiatric symptoms improved by structurally reviewing the prescriptions of nursing home patients with dementia every 6 months. Regarding all psychotropic prescriptions combined, overall appropriateness improved; on the level of domains, the evaluation and the therapy duration improved.

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

Table 2. Observed Appropriate Psychotropic drug use In Dementia index sum score means of all psychotropic drug prescriptions at baseline, 6, 12 and 18 months

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

PDs, psychotropic drugs, CI, 95% confidence interval.

Table 3. Effect of structural medication reviews on the Appropriate Psychotropic drug use In Dementia index sum score, indication score, evaluation score and therapy duration score of psychotropic drug prescriptions[a]

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

CI, 95% confidence interval, n.a., not applicable, TR, theoretical range. *Significant influence on regression $P < 0.05$.

[a]Analyses were performed on cluster-level. Analyses on antiepileptics were excluded, considering the small sample size ($n = 13$ at baseline). Adjacent small dementia special care units sharing staff and corridors that had few participating patients, i.e. ≤3 patients participating on each unit at one or more of the measurement points, were grouped. This was the case for three different nursing homes: two, three, five and five dementia special care units, respectively, with shared staff and corridors were grouped into larger clusters encompassing at least nine patients participating at baseline, after 6, 12 or 18 months.

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

Strengths and limitations

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

A limitation is the low participation rate in some dementia special care units, resulting in a few small clusters. Furthermore, the overall sample size of some psychotropic drug groups was small; therefore, group specific reports should be interpreted carefully.

Additionally, few small 'clusters' involved should not have been regarded separate entities in the first place, because they shared staff and corridors, so that the risk of contamination was eminent. More specifically, dementia special care units in the Netherlands have various sizes, i.e. 5–30 patients. Small units share staff and corridors. Although the decision to merge these units was made after the data were collected, this was well before statistical analyses had started. It is unfortunate that we did not realise this hidden clustering a priori, but we feel that the current analysis reflects the real clustering present in our study best.

Another limitation may be that the outcome measurement, the Appropriate Psychotropic drug use In Dementia index, is partly based on Dutch drug formularies, implying for instance that some psychotropic drugs cannot be scored as inappropriate for therapy duration. Further, it uses patient records. As a result, the score may be affected by suboptimal recordkeeping. However, good recordkeeping can be considered as an indispensable prerequisite for judging the appropriateness of prescription; physicians need good recordkeeping to evaluate the psychotropic drug prescriptions [17].

Clinical implications

The clinical use of off-label prescriptions is widespread [26]; many different psychotropic drugs are prescribed to individual patients with similar neuropsychiatric symptoms [19, 27]. Psychotropic drug prescriptions for neuropsychiatric symptoms in dementia were rated as appropriate when guidelines recommended these specific prescriptions for a neuropsychiatric symptom, but even when there is maximum guideline adherence, there still is limited evidence for the efficacy of

treatment [25] and, therefore, psychotropic drugs should be regularly evaluated. Additionally, antipsychotics, anxiolytics and hypnotics/sedatives are used too long [8, 19].

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

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

Key points

- We advise the implementation of a structured, repeated medication review with pharmacist, physician and nurse.
- Reviewing medication can improve the appropriateness of psychotropic drug prescriptions in patients with dementia.
- This study shows that the implementation of structured biannual medication reviews (including education) is effective

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Conflict of interest

None declared.

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