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Time trends in psychotropic drug prescriptions in Dutch nursing home residents with dementia between 2003 and 2018

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Abstract

Objective: Several European studies investigated the trends in psychotropic drug prescriptions (PDPs) among nursing home (NH) residents and reported a decline in antipsychotics prescriptions. Since the Dutch long-term care system differs from other European systems (e.g. higher threshold for NH admission and trained elderly care physicians), this study explores the trends in PDPs in Dutch NH residents with dementia.

Methods: The study used data from nine studies, comprising two cross-sectional studies, one cohort study, and six cluster-randomized controlled trials, collected in Dutch NHs between 2003 and 2018. With multilevel logistic regression analysis, NHs as a random effect, we estimated the trends in PDPs overall and for five specific psychotropic drug groups (antipsychotics, antidepressants, anxiolytics, hypnotics, and anti-dementia drugs), adjusting for confounders: age, gender, severity of dementia, severity of neuropsychiatric symptoms, and length of stay in NHs.

Results: The absolute prescription rate of antipsychotics was 37.5% in 2003 and decreased (OR = 0.947, 95% CI [0.926, 0.970]) every year. The absolute prescription rate of anti-dementia drugs was 0.8% in 2003 and increased (OR = 1.162, 95% CI [1.105, 1.223]) per year. The absolute rate of overall PDPs declined from 62.7% in 2003 to 40.4% in 2018.

Conclusions: Among Dutch NH residents with dementia, the odds of antipsychotics prescriptions decreased by 5.3% per year while the odds of anti-dementia drug prescriptions increased by 16.2%. There were no distinct trends in antidepressants, anxiolytics, and hypnotics prescriptions. However, overall PDPs were still high. The PDPs in NH residents remain an issue of concern.

KEYWORDS
dementia, nursing home, psychotropic drugs

Key points

- This study used data from nine studies that were collected from different nursing homes throughout the Netherlands, contributing to this study's external validity.
- When analysing the trends in psychotropic drug prescriptions (PDPs), this study was adjusted for severity of dementia and severity of neuropsychiatric symptoms to better reflect the actual time trends in PDPs.
- The antipsychotics prescriptions among Dutch nursing home residents with dementia decreased and the anti-dementia drug prescriptions increased slightly between 2003 and 2018. The overall PDPs decreased but were still high.

1 | INTRODUCTION

Neuropsychiatric symptoms (NPSs) are highly prevalent in people with dementia. It is estimated that around 79% of nursing home (NH) residents diagnosed with dementia have at least one NPS.[1] NPSs reduce the patients' quality of life and cause a burden to their caregivers.[2,3] Therefore, appropriate management of NPSs is necessary.

For the treatment of NPSs, guidelines recommend psychosocial interventions as first-line treatment, whereas pharmacological interventions, such as psychotropic drugs, are only advised as second-line treatment.[4-6] The effectiveness of psychotropic drugs is unclear, while the drugs are associated with serious adverse effects.[5] The European Medicines Agency (EMA) concluded that there is an increased risk of cerebrovascular adverse events and mortality in elderly patients with dementia who receive antipsychotics.[7] The US Food and Drug Administration issued black-box warnings about atypical antipsychotics in 2005 and about conventional antipsychotics in 2008.[8] The warnings related to antipsychotics were also published by the EMA, the UK, France, and other countries.[7,9,10] Antidepressants, more specifically selective serotonin reuptake inhibitors (SSRIs), were initially considered safe for older people. However, one study found an association between antidepressants and the risk of injurious falls.[11]

Regardless of the recommendations and warnings, the prescription of psychotropic drugs, especially of antipsychotics and antidepressants, is still prevalent in European NHs with percentages varying from 12% to 59% and from 19% to 68%, respectively.[12] Since the first warnings and recommendations in 2004,[13] several European studies investigated NPSs and psychotropic drug prescriptions (PDPs) among NH residents. A Norwegian study explored the trends in PDPs among NH residents using data from six cross-sectional studies that were conducted in NHs between 1997 and 2009. The study found that the prescriptions of antidepressants (from 31.5% to 50.9%), anxiolytics (from 14.9% to 21.9%), and hypnotics (from 14.5% to 22.9%) increased.[14] The prescription of antipsychotics was fairly stable over time: 23.4% in 1997 and 22.9% in 2009.[14] Another Norwegian study, which included two cohort studies that were carried out between 2004 and 2011, showed a significant decline in antipsychotics prescriptions (from 24.1% to 16.7%) among NH residents with dementia.[15] Other studies also identified a decrease in the

prescription of antipsychotics for NH residents in Finland and the UK.[16,17]

In this study, we looked closer at the trends in PDPs in Dutch NH residents with dementia, given the growing concerns around these drugs in recent years. The Dutch long-term care system differs from other European care systems. The Dutch government raised the threshold for admission to a NH in 2015 and the Netherlands has trained elderly care physicians who are mostly hired by long-term care organizations.[18] The excellently trained Dutch elderly care physicians ensure that hospitalisation at the end-of-life stage is unnecessary and 92.3% of older people with dementia died in a long-term care facility in the Netherlands in 2003, which is significantly higher than the percentages in the UK and Belgium.[19] Since a higher proportion of older people with dementia live in NHs at the end-of-life stage, the prescription rates of psychotropic drugs might differ from those in other European countries. The Dutch elderly care physicians are specifically trained to treat geriatric diseases, which may result in more appropriate and perhaps fewer PDPs in Dutch NHs.

Therefore, this study aimed to investigate time trends in PDPs in Dutch NH residents with dementia. Following the updated safety regulations, guideline recommendations, and the ongoing focus on health risks associated with antipsychotics in recent years, non-pharmacological treatments have gained more attention.[6,7,13,20] We hypothesised that the prescription of antipsychotics decreased from 2003 to 2018 in Dutch NH residents with dementia.

2 | METHODS

This study used convenience sampling and selected nine studies that were carried out between 2003 and 2018 in Dutch NHs that agreed to share data with us to analyse trends in PDPs in Dutch NH residents with dementia. The nine studies comprised two cross-sectional studies (WAAL Behaviour in Dementia-1,WAALBED-1[21]; PRescription Optimization of PDs in Elderly nuRsing home patients with dementia, PROPER-1 study[22]), one cohort study (WAALBED-2[23]), and six cluster-randomized controlled trials (Grip on challenging behaviour study, GRIP[24]; Dementia-Care Mapping, DCM[25]; *STApsgewijs Onbegrepen gedrag en Pijn bij dementie de baas!*, STA OP! (a stepwise approach to managing pain and challenging behaviours in residents

with advanced dementia)[26]; PROPER-2[27]; Reducing inappropriate PDPs in nursing home residents with dementia, RID[28]; Soundscape improvement with MoSART+, which combines the use of the smartphone application MoSART and specifically trained sound-ambassadors to reduce NPSs in nursing home patients with dementia, MoSART+ [unpublished]).

All residents included in these studies had a diagnosis of dementia/major neurocognitive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (4th/5th editions). A few studies added additional inclusion criteria. The DCM study only included residents with at least one NPS as measured by the Neuropsychiatric Inventory Nursing Home version. In the *STA OP!* study, residents with pain and/or challenging behaviour and a Global Deterioration Scale (GDS) score greater than or equal to 5, which corresponds to moderate dementia, were included. The WAALBED-1 study excluded terminally ill residents and the WAALBED-2 study excluded residents who had life-threatening diseases. The DCM study only included residents with an estimated life expectancy of more than 6 weeks. The RID study used life expectancy of more than 3 months as inclusion criteria. For the WAALBED-1 study, the WAALBED-2 study, the DCM study, and the GRIP study, residents with GDS scores lower than or equal to three or with a missing GDS score were excluded.[29]

3 | DATA EXTRACTION

For the cohort study and the cluster-randomized controlled trials, only baseline data were extracted. Resident-level data included demographic data (age and gender), length of stay in NHs (measured in months), dementia severity, the severity of NPSs, and PDPs. The median date of data collection for each study is shown in Table 1.

Some residents were included in more than one of the WAALBED-1, WAALBED-2, DCM, and GRIP studies. These residents were identified and only counted in the most recently performed study. The total number of residents from the nine studies was 3719.

Dementia severity was assessed using the GDS in six studies, the Cognitive Performance Scale (CPS) in the RID study, and the Clinical Dementia Rating (CDR) scale in the MoSART+ study. There was no information about dementia severity in PROPER-1. The GDS distinguishes seven stages of cognitive decline in dementia, ranging from no cognitive decline (stage 1) to very severe cognitive decline (stage 7).[30] The CPS rates cognitive status from 0 (intact) to 6 (very severe impairment).[31] The CDR is a 5-point dementia scale, ranging from 0 (healthy), 0.5 (questionable dementia), 1 (mild dementia) to 3 (severe dementia).[32] Since no specific rules for converting CDR scores or CPS scores to GDS scores were found and most of the studies (6 out of 9) used the GDS, we decided to impute GDS scores for the remaining studies. The detailed procedure is described in the statistical analysis section.

The severity of NPSs was assessed using the Neuropsychiatric Inventory Nursing Home version (NPI-NH) in seven studies and with the Neuropsychiatric Inventory Questionnaire version (NPI-Q) in the two PROPER studies. NPI-NH and NPI-Q are based on the Neuropsychiatric Inventory (NPI) and comprise 12 NPS domains that are common in dementia.[33] For each symptom, the frequency and severity are assessed in the NPI-NH, while in the NPI-Q, each symptom is only assessed for severity. The NPI-Q symptom severity score is strongly correlated with the NPI symptom severity score. The inter-scale item correlation of each symptom's severity score between NPI and NPI-Q ranged from 0.71 to 0.93.[34] Since NPI-NH and NPI are identical in content, we assumed that the NPI-NH symptom severity score and the NPI-Q symptom severity score are also strongly correlated. Thus, for studies using the NPI-NH, only symptom severity scores were used to establish one severity score for NPSs, making it comparable to the NPI-Q symptom severity score, which ranged from 0 to 36.

Psychotropic drugs were classified using the Anatomical Therapeutic Chemical (ATC) classification for antipsychotics (N05A), anxiolytics (N05B), hypnotics (N05C), antidepressants (N06A), and anti-dementia drugs (N06D). The 'as needed' drug prescription was not included. Anticonvulsants were not considered in this study since we could not retrieve the reason for the prescription (epilepsy or NPSs).

4 | STATISTICAL ANALYSIS

In the descriptive analysis section, the mean and the standard deviation (SD) were calculated for normally distributed continuous variables, while the median and the quartiles were calculated for non-normally distributed continuous variables. Frequencies and percentages were calculated for categorical variables.

Due to differences in assessment strategies among the studies, some variables were missing. GDS scores were not assessed in three studies (PROPER-1, RID, and MoSART+). In the *STA OP!* study, the symptom severity scores of the last two domains (sleep and night-time behaviour disorders, and appetite and eating changes) were missing and we only assessed the presence of these two symptoms. Rather than analysing the cases without missing values, which might bias the estimates, all missing data were imputed under the missing at random (MAR) assumption per item. The missing values were modelled as a function of the values of all the observed variables. Five data sets with imputed values for missing items on each variable were obtained using the Multivariate Imputation by Chained Equations (MICE) command in R.[35] This program uses Fully Conditional Specification (FCS), implemented by the MICE algorithm to estimate missing values. Each variable had its own imputation model. Five data sets containing imputed values were generated and the results of multilevel logistic regression analysis performed on each data set were pooled according to Rubin's rules.[36]

Both logistic regression and multilevel logistic regression models (with the nursing home as a random effect) were applied, with PDPs, including overall psychotropic drugs, antipsychotics, antidepressants, anxiolytics, hypnotics, and anti-dementia drugs, as a dependent variable. The primary explanatory variable included in each model was calendar time, which was expressed in years. Data collection started

TABLE 1 Residents' characteristics of the nine Dutch studies on psychotropic drug use in nursing home (NH) residents with dementia from 2003 to 2018. N = 3719

Residents characteristics	WAALBED-1[20]	WAALBED-2[22]	STA OP![25]	DCM[24]	GRIP[23]	PROPER-1[21]	PROPER-2[26]	RID[27]	MoSART+[unpublished]
Type of study	Cross-sectional	Cohort	RCT	RCT	RCT	Cross-sectional	RCT	RCT	RCT
Median date data collection (baseline)	Jun 2003	Oct 2006	Oct 2010	Oct 2010	Jun 2011	Apr 2012	Nov 2012	Dec 2016	Aug 2018
N	1294	288	288	171	323	557	123	576	99
Age (mean, SD)	82.7 (7.8)	83.2 (7.2)	83.8 (7.1)	83.3 (6.5)	83.8 (7.6)	84.4 (6.6)	82.5 (8.0)	83.7 (7.6)	86.2 (6.8)
% Female	80.1	76.0	71.9	74.3	71.2	73.6	73.2	73.6	75.8
Length of stay in NHs in months (median, quartiles)	20.1 (9.2, 39.3)	26.0 (15.1, 53.5)	22.4 (10.6, 40.4)	15.3 (3.7, 32.8)	20.3 (10.2, 40.4)	19.6 (9.0, 36.9)	8.6 (4.6, 22.9)	19.7 (9.0, 35.1)	23.9 (8.4, 44.8)
Dementia severity									
GDS/CDR/CPS									
GDS (mean, SD)	6.05 (0.8)	5.9 (0.9)	6.2 (0.6)	5.9 (1.0)	5.9 (0.6)	-	5.4 (1.1)	-	-
CDR (median, quartiles)	-	-	-	-	-	-	-	-	2.0 (1.0, 3.0)
CPS (Median, quartiles)	-	-	-	-	-	-	-	3.0 (3.0, 5.0)	-
Neuropsychiatric symptoms									
NPI-NH total score (median, quartiles) [score range 0-144]	18.0 (8.0, 30.0)	12.0 (5.0, 24.0)	11.5[b] (4.0, 21.3)	10.0 (2.0, 20.0)	20.0 (8.5, 37.0)			18.0 (8.0, 30.0)	12.0 (6.0, 25.0)
NPI-NH Symptom severity total score[a]/NPI-Q total score (median, quartiles) [score range 0-36]	5.5 (3.0, 9.0)[a]	4.0 (2.0, 8.0)[a]	4.0[b] (1.0, 7.0)[a]	3.0 (1.0, 7.0)[a]	7.0 (4.0, 12.0)[a]	6.0 (3.0, 11.0)	4.0 (1.0, 9.0)	6.0 (3.0, 10.0)[a]	5.0 (2.0, 8.0)[a]
Psychotropic drug use, N (%)									
Overall psychotropic drug ≥1	811 (62.7)	166 (57.6)	188 (66.7)	62 (50.8)	181 (58.6)	332 (59.9)	57 (46.3)	311 (54.0)	40 (40.4)
Antipsychotics ≥1	485 (37.5)	94 (32.6)	102 (36.2)	30 (24.6)	86 (27.8)	140 (25.3)	29 (23.6)	147 (25.5)	14 (14.1)
Antidepressants ≥1	354 (27.4)	71 (24.7)	67 (23.8)	27 (22.1)	101 (32.7)	161 (29.1)	22 (17.9)	127 (22.0)	24 (24.2)
Anxiolytics ≥1	202 (15.6)	52 (18.1)	96 (34.0)	15 (12.3)	48 (15.5)	83 (15.0)	21 (17.1)	106 (18.4)	5 (5.1)
Hypnotics ≥1	195 (15.1)	36 (12.5)	56 (19.9)	8 (6.6)	34 (11.0)	74 (13.4)	14 (11.4)	91 (15.8)	7 (7.1)
Anti-dementia drugs ≥1	10 (0.8)	13 (4.5)	25 (8.9)	6 (4.9)	27 (8.7)	80 (14.4)	8 (6.5)	48 (8.3)	6 (6.1)

Note: STA OP!'s NPI-NH total score and NPI-NH symptom severity total score.

Abbreviations: CDR, Clinical Dementia Rating Scale; CPS, Cognitive Performance Scale; GDS, Global Deterioration Scale; NPI-NH, Neuropsychiatric Inventory Nursing Home version; NPI-Q, Neuropsychiatric Inventory Questionnaire version.

[a]We rescaled the NPI-NH only use severity scores and combined it with the NPI-Q.

[b]The STA OP! study only assessed 10 behavioral domains of the NPI-NH.

in June 2003, based on which the calculated number of years was obtained for every resident. Multivariate adjusted logistic regression analysis was performed on both the logistic regression model and the multilevel logistic regression model. In the multivariate analysis, the effects of calendar time on PDPs were adjusted for age, sex, length of NH stay, severity of dementia, and the severity of NPSs. For the multilevel analysis, all independent variables were centred on the mean. The results were presented as odds ratios with 95% confidence intervals, representing the chance of changes per year compared to the previous year. The fit of the models was measured by the area under the ROC Curve (AUC).

In a sensitivity analysis, we took cohort effects into account that might have caused a gradual change in residents' PDPs over time. As in a previous study,[37] NPSs were categorised into depression, anxiety, apathy, clustered symptoms, such as psychosis (hallucinations and/or delusions), and agitation (agitation, disinhibition, and/or irritability). We selected the subgroups of residents based on NPSs categorisations and executed the multilevel logistic regression model for each subgroup.

The descriptive analysis was executed in SPSS v25 and the imputation and the various logistic regressions were executed in R v4.0.2.

5 | RESULTS

The study size varied widely among the studies, from 99 to 1294 subjects (Table 1). The mean age varied between 82.7 and 86.2 years. The proportion of female residents ranged from 71.2% to 80.1%. The median length of stay varied from 8.6 to 26.0 months. The GDS, CDR, and CPS scores showed that most of the residents included in the studies had moderate to severe dementia (detailed descriptions of the dementia severity levels can be found in Supplementary Table 1). The median severity scores for NPSs ranged between 3.0 and 7.0.

The absolute rate of overall PDPs and of antipsychotics prescriptions decreased from 63% in 2003 to 40% in 2018 and from 38% in 2003 to 14% in 2018, respectively. The prescription rate of anti-dementia drugs increased from 1% in 2003 to 6% in 2018. The prescription rates of antidepressants, anxiolytics, and hypnotics fluctuated over the years without clear trends.

6 | LOGISTIC REGRESSION ANALYSIS

In the multilevel logistic regression, a significant crude effect of time on overall PDPs (OR = 0.968, 95% CI [0.949, 0.988]) and on antipsychotics prescriptions (OR = 0.951, 95% CI [0.931, 0.971]) was found, indicating a decrease in drug prescriptions over time (Table 2). A significant crude effect of time on anti-dementia drug prescriptions (OR = 1.162, 95% CI [1.105, 1.223]) was found. After adjusting for age, gender, length of stay in NHs, severity of dementia, and severity of NPSs, a significant adjusted effect of time on overall PDPs (OR = 0.962, 95% CI [0.940, 0.985]), antipsychotics prescriptions

(OR = 0.947, 95% CI [0.926, 0.970]), and anti-dementia drug prescriptions (OR = 1.162, 95% CI [1.105, 1.223]) were found. There were significant slightly negative trends in overall PDPs and antipsychotics prescriptions and a significant positive trend for anti-dementia drug prescriptions. The odds of the overall PDPs and antipsychotics prescriptions decreased by approximately 3.8% and 5.3% per year compared to the previous year, respectively, over time. While the odds of anti-dementia drug prescriptions increased by 16.2% per year compared to the previous year (with an initial anti-dementia drug prescription rate of 0.8% in the year 2003), no significant trends were found for the prescriptions of antidepressants, hypnotics, and anxiolytics. AUC reflected that adjusting for confounders improved the fitness of the model.

The sensitivity analysis was performed for the multilevel logistic regression model. The categorised NPI symptoms showed no impact on the trends (results were not presented in the tables).

7 | DISCUSSION

To our knowledge, this is the first study to explore the longitudinal trends in PDPs in Dutch NH residents with dementia. We found a slight but significant decrease of the odds of antipsychotics prescriptions, approximately 5% per year, and an increase of the odds of anti-dementia drug prescriptions, 16% per year. The time trends in antipsychotics and anti-dementia drugs remained statistically significant after adjusting for age, gender, length of stay in NHs, severity of dementia, and severity of NPSs. The prescriptions of other psychotropic drugs did not show significant time trends. The overall rate of PDPs decreased from 62.7% in 2003 to 40.4% in 2008, which was still high.

Previous longitudinal studies showed decreasing prescription rates of antipsychotics both in the general population with dementia and in nursing home residents.[14-17] In line with those studies, we also found a decrease in antipsychotics prescriptions. Reasons for the decrease in antipsychotics prescriptions are likely to be changes to the drug prescribing policies of physicians following the warnings from the EMA and the adjusted treatment guidelines.[4,7,13] In addition, many studies focused on psychosocial interventions and found them to be effective in dealing with NPSs. These interventions were related to a substantial decrease in the use of antipsychotics.[5,25,26] Also, governments and lobby organizations took actions in recent years to raise public awareness about using fewer psychotropic drugs.[6,13,20] In the guidelines of the Dutch Association of Elderly Care Physicians,[6] non-pharmacological interventions are recommended as first-line treatment. They also suggest that physicians should be very cautious when prescribing psychotropic drugs, should monitor the effect and side effects systematically, and should stop the PDPs if necessary.[6] This could be the reason for the drop in antipsychotics prescriptions and overall PDPs. The greater availability of non-pharmacological interventions in NHs in recent years could also explain the decrease in antipsychotics prescriptions and overall PDPs.

TABLE 2 Regression coefficients with 95% CI from logistic regression and multilevel logistic regression models with the (specific) psychotropic drug groups as an outcome variable N = 3719

	Psychotropics		Antipsychotics		Antidepressants	
	Logistic regression OR (95% CI)	Multilevel model[a] OR (95% CI)	Logistic regression OR (95% CI)	Multilevel model[a] OR (95% CI)	Logistic regression OR (95% CI)	Multilevel model[a] OR (95% CI)
Crude effect:						
Intercept	1.726** (1.551–1.922)	1.784** (1.492–2.134)	0.612** (0.548–0.682)	0.592** (0.4933–0.7108)	0.384** (0.342–0.432)	0.385** (0.326–0.456)
Time (per year)[b]	0.971** (0.959–0.984)	0.968* (0.949–0.988)	0.951** (0.937–0.964)	0.951** (0.931–0.971)	0.987 (0.973–1.001)	0.985 (0.966–1.004)
AUC	0.541 (0.541, 0.541)	0.627 (0.625, 0.630)	0.572 (0.572, 0.572)	0.641 (0.640, 0.642)	0.518 (0.518, 0.519)	0.617 (0.615, 0.620)
Adjusted effect:						
Intercept	14.455** (5.071–41.205)	14.218* (4.558–44.350)	1.426 (0.505–4.028)	1.296 (0.426–3.947)	1.884 (0.645–5.499)	1.793 (0.590–5.452)
Time (per year)[b]	0.965** (0.952–0.978)	0.962* (0.940–0.985)	0.947** (0.933–0.961)	0.947** (0.926–0.970)	0.984* (0.969–0.999)	0.983 (0.964–1.003)
Age (years)	0.974** (0.964–0.983)	0.974** (0.965–0.984)	0.981** (0.971–0.991)	0.982** (0.972–0.992)	0.979** (0.970–0.989)	0.980** (0.970–0.990)
Gender (female)[c]	0.913 (0.775–1.075)	0.928 (0.785–1.097)	0.739** (0.623–0.875)	0.738** (0.621–0.878)	1.186 (0.991–1.419)	1.212* (1.011–1.453)
Length of stay in NHs (months)	0.993** (0.990–0.995)	0.992** (0.989–0.995)	0.994** (0.991–0.998)	0.994** (0.991–0.998)	0.997 (0.994–1.000)	0.997 (0.994–1.0003)
Severity of dementia	0.982 (0.891–1.082)	0.969 (0.866–1.084)	1.119* (1.022–1.226)	1.101 (0.995–1.219)	0.954 (0.852–1.069)	0.952 (0.843–1.075)
Severity of NPSs	1.089** (1.073–1.104)	1.098** (1.081–1.114)	1.075** (1.061–1.090)	1.083** (1.068–1.099)	1.056** (1.042–1.070)	1.057** (1.043–1.072)
AUC	0.655 (0.655,0.656)	0.699 (0.695,0.702)	0.656 (0.652, 0.660)	0.702 (0.701, 0.702)	0.602 (0.601,0.604)	0.644 (0.640, 0.650)

	Anxiolytics		Hypnotics		Anti-dementia	
	Logistic regression OR (95% CI)	Multilevel model[a] OR (95% CI)	Logistic regression OR (95% CI)	Multilevel model[a] OR (95% CI)	Logistic regression OR (95% CI)	Multilevel model[a] OR (95% CI)
Crude effect:						
Intercept	0.200** (0.174–0.230)	0.194** (0.149–0.253)	0.173** (0.149–0.200)	0.147** (0.106–0.205)	0.024** (0.018–0.032)	0.016** (0.009–0.026)
Time (per year)[b]	1.006 (0.989–1.022)	0.9999 (0.971–1.030)	0.992 (0.975–1.011)	0.989 (0.954–1.026)	1.135** (1.103–1.168)	1.162** (1.105–1.223)
AUC	0.501 (0.501, 0.501)	0.684 (0.682, 0.687)	0.517 (0.516, 0.517)	0.724 (0.722, 0.725)	0.684 (0.684, 0.684)	0.801 (0.799, 0.803)
Adjusted effect:						
Intercept	0.327 (0.101–1.059)	0.335 (0.092–1.222)	0.354 (0.098–1.271)	0.270 (0.066–1.106)	8.461* (1.494–47.933)	5.412 (0.768–38.113)
Time (per year)[b]	1.007 (0.990–1.025)	0.9999 (0.968–1.033)	0.989 (0.971–1.008)	0.987 (0.951–1.024)	1.132** (1.098–1.167)	1.162** (1.105–1.223)
Age (years)	0.982* (0.970–0.993)	0.983* (0.971–0.995)	0.992 (0.979–1.004)	0.993 (0.980–1.007)	0.957* (0.940–0.974)	0.952* (0.934–0.971)
Gender (female)[c]	1.128 (0.914–1.392)	1.167 (0.938–1.451)	0.784* (0.633–0.971)	0.763* (0.610–0.955)	0.646* (0.481–0.868)	0.649* (0.478–0.881)
Length of stay in NHs (months)	0.999 (0.995–1.002)	0.999 (0.995–1.002)	0.992** (0.988–0.997)	0.993** (0.988–0.997)	0.978** (0.970–0.987)	0.977** (0.968–0.986)

TABLE 2 (Continued)

| | Anxiolytics | | Hypnotics | | Anti-dementia | |
	Logistic regression OR (95% CI)	Multilevel model[a] OR (95% CI)	Logistic regression OR (95% CI)	Multilevel model[a] OR (95% CI)	Logistic regression OR (95% CI)	Multilevel model[a] OR (95% CI)
Severity of dementia	1.091 (0.964–1.24)	1.040 (0.898–1.205)	1.022 (0.907–1.151)	1.010 (0.884–1.154)	0.728* (0.612–0.865)	0.789* (0.638–0.977)
Severity of NPSs	1.067** (1.051–1.083)	1.080** (1.062–1.097)	1.037** (1.020–1.054)	1.044** (1.025–1.062)	1.042** (1.017–1.066)	1.045** (1.019–1.071)
AUC	0.624 (0.618, 0.630)	0.718 (0.717, 0.720)	0.592 (0.587, 0.597)	0.736 (0.735, 0.738)	0.775 (0.766, 0.784)	0.846 (0.843, 0.849)

[a]The NH is used as a random effect.
[b]In period: June 2003–Aug 2018.
[c]Female is used as a reference group an indication of logistic regression model fitness.
Significance levels: $*p < 0.05$, $**p < 0.001$.

Previous studies rarely adjusted for severity of dementia and severity of NPSs, variables that might influence the PDPs. More severe NPSs[38,39] and dementia[38] are reported to be associated with higher PDPs. In our study, we were able to correct for cohort effects by not only correcting for demographic characteristics but also for severity of dementia and severity of NPSs. Therefore, the decrease in antipsychotics prescriptions found in this study is likely to reflect actual trends better than previous studies. Consistent with previous studies,[38,39] this study found a positive association between the severity of NPSs and all subgroups of PDPs. The severity of dementia was shown to be negatively associated with anti-dementia drugs, after adjusting for the severity of NPSs. The reason might be that most of the patients included in this study had moderate to severe and very severe dementia (Supplementary Table 1). Stopping the prescription of anti-dementia drugs should be considered if the person has severe dementia, when anti-dementia drugs are of less cognitive benefit.[40]

An increase in anti-dementia drug prescriptions was found in this study. A Danish study showed a persistent use of anti-dementia drugs among NH residents, 24% at the baseline and 28% at the end of 3-year follow-up.[41] Similarly, a study conducted in the UK showed an increased prescription rate of anti-dementia drugs between 2005 and 2015.[17] Compared with these two studies, the absolute prescription rate of anti-dementia drugs in the present study was lower, ranging from 0.8% to 14.4%. This might be due to a different study population. Most of the residents in our study had moderate to severe dementia. Severe dementia might lead to the stopping of the use of anti-dementia drugs.[40] Although the prescription rate of anti-dementia drugs is low, it increased over time. One reason could be that anti-dementia drugs, except for donepezil, became part of the reimbursement system in the Netherlands in the year 2006.[42] Another reason might be that elderly care physicians keep prescribing anti-dementia drugs to older people with severe dementia. The British Association for Psychopharmacology stated that anti-dementia drugs should not be stopped just because the severity of dementia increases,[43] while the European guidelines did not give a clear suggestion as to when to withdraw anti-dementia drugs.[44]

No significant time trends were found for the prescriptions of antidepressants, anxiolytics, and hypnotics in this study. Inconsistent trends were found for prescriptions of these subgroups of psychotropic drugs in previous studies.[14-17] Since these PDPs did not increase, while the antipsychotics prescriptions decreased, we assume that the elderly care physicians did not prescribe compensatory medications to treat NPSs that were previously treated with antipsychotics. Similarly, a Norwegian study also reported that physicians did not increase alternative medications to treat NPSs.[15]

A strength of the study is that the recruited residents in the nine studies were from different NHs throughout the Netherlands, contributing to the study's external validity. In addition, we adjusted our results using severity of dementia and severity of NPSs in the multilevel logistic regression. This helped us to decide

whether the trends in PDPs might be due to the change in clinical practice or merely to the differences in severity of dementia or severity of NPSs.

However, this study used data from several studies that were conducted for other purposes. Consequently, there were differences in the scales that were used and in some inclusion criteria. We tried to limit the bias by using NH as a random effect when analysing the data. The chosen studies included all types of dementia. This might be a limitation due to the differences in prevalence rates of NPSs among the various types of dementia and, therefore, prescriptions of psychotropic drugs. Some NHs may have been included in more than one study and there may be some overlap of older adults in different studies. Since the data we used were pseudonymous, we are not able to check for additional overlap. We assume that the number of overlaps is low since there were only 13 participants who overlapped out of 2076 older adults from the WAALBED-1 study, the WAALBED-2 study, the DCM study, and the GRIP study. The indicators for the prescriptions of psychotropic drugs were not recorded in these studies, therefore, we could not adjust for them. Only one of the included studies registered comorbidities. Therefore, we could not assess the impact of comorbidities, such as pain, on PDPs. Furthermore, the studies only focused on consistently prescribed drugs. Therefore, data might differ from the actual use due to 'as needed' drug intake.

8 | CONCLUSION

Among Dutch nursing home residents with dementia, the prescriptions of antipsychotics decreased and the prescriptions of anti-dementia drugs increased slightly between 2003 and 2018. The decrease in antipsychotics without compensatory increases of antidepressants, anxiolytics, or hypnotics prescriptions can be considered a favourable practice trend. The prescription rate of overall psychotropic drugs decreased but was still high. We are on the right track. And we can likely do better by reducing the prescriptions of antidepressants, anxiolytics, and hypnotics. Elderly care physicians should regularly assess the effectiveness and occurrence of side effects when prescribing psychotropic drugs to residents with dementia and should stop the prescription if necessary. Further studies could specify the types of anti-dementia drugs, distinguishing between cholinesterase inhibitors and memantine, to determine whether the trends in anti-dementia drug prescription are appropriate.

CONFLICT OF INTEREST
All authors declared no conflicts of interest.

AUTHOR CONTRIBUTIONS
Sarah Janus and Sytse Zuidema designed the study, obtained the data from the original authors, and assisted in revising the manuscript. Jiamin Du cleaned the data, performed the descriptive analysis, interpreted the data, and wrote the manuscript. Brenda Voorthuis carried out the regression analysis and helped with the interpretation. Jeannette van Manen, Wilco Achterberg, Martin Smalbrugge, Sandra Zwijsen, Debby Gerritsen, and Raymond Koopmans were the principal investigators of the original studies, of which the data were used. They also revised the manuscript and provided useful comments.

DATA AVAILABILITY STATEMENT
This study used data from 9 studies collected in Dutch nursing homes between 2003 and 2018. It would be best if you asked for permission from the authors of the original studies to get access to the data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.