JAMDA xxx (2019) 1–8

JAMDA

journal homepage: www.jamda.com

Original Study

Cluster-Controlled Trial of an Intervention to Improve Prescribing in Nursing Homes Study

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Keywords:
Nursing homes
appropriateness of prescribing
interdisciplinary collaboration
medication review
complex intervention

A B S T R A C T

Objectives: To investigate the impact of a complex multifaceted intervention on the appropriateness of prescribing for Belgian nursing home (NH) residents.
Design: A multicenter, nonblinded, cluster-randomized controlled trial, with randomization at the NH level, was set up [Cluster-Controlled Trial of an Intervention to Improve Prescribing in Nursing Homes (COME-ON) Study]. The complex intervention consisted of repeated interdisciplinary case conferences (ICCs) involving the general practitioner, pharmacist, and nurse, aimed at performing a medication review for each NH resident included. The ICCs were supported by a blended training program and local interdisciplinary meetings (discussion of the appropriate use of specific medication classes at the NH level). Control NHs delivered usual care. (isrctn.com: ISRCTN66138978).
Setting and participants: Belgian NHs with at least 35 NH residents were eligible to participate. Eligible residents were those aged 65 years or over, not receiving palliative care, and being treated by a participating general practitioner.
Measures: The primary outcome measure related to appropriateness of prescribing at resident level and was considered successful when at least 1 potentially inappropriate medication (PIM) or potential prescribing omission (PPO) present at baseline had been solved at the end of study and when there were no new PIMs or PPOs at the end of study compared with baseline. Secondary outcomes included clinical outcomes, medication use, criterion-specific prevalence of PIMs and PPOs, and ICC outcomes.
Results: In total, 54 NHs (24 intervention; 30 control) and 1804 NH residents (847 intervention; 957 control) participated. Using a 3-level mixed-effects model accounting for data clustering, a significant effect in favor of the intervention was observed (odds ratio 1.479 [95% confidence interval 1.062-2.059, $P = .021$]). There was no significant difference between groups for most clinical outcomes. The median number of medications did not change over time in either group.
Conclusions and implications: The complex multifaceted intervention tested in the COME-ON study successfully improved appropriateness of prescribing in NHs.

Prescribing and selecting appropriate medication for older people is a challenging process. Potentially inappropriate prescribing (PIP), which encompasses underprescribing, overprescribing, and misprescribing, is therefore widespread.[1] Morin et al reported that almost one-half of nursing home (NH) residents are exposed to at least 1 PIP.[2] In a recent systematic review, Storms et al showed that

The authors declare no conflicts of interest.
The study was funded by the National Institute for Health and Disability Insurance (NIHDI). The funding body had a limited role in the design but had no role in data collection, implementation, analysis, or the decision to publish the results. PA and GS were paid by the NIHDI.
This study has been registered at http://www.isrctn.com/ (trial registration number: ISRCTN66138978)

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https://doi.org/10.1016/j.jamda.2019.06.006
1525-8610/

application of the Beers and STOPP (Screening Tool of Older Person's Prescriptions) criteria [allowing the identification of potentially inappropriate medication (PIM)] resulted in a median prevalence of PIP of 46.5% and 61.1%, respectively. Application of the START (Screening Tool to Alert doctors to Right Treatment) criteria [allowing the identification of potential prescribing omissions (PPO)] resulted in a median prevalence of 30.5%-74.0%.[3]

The presence of PIP has been associated with adverse drug reactions,[4,5] increased healthcare utilization,[6–10] and even death.[6–8,11] It has, therefore, become an important public health concern.

Over the last decade, various interventions to improve appropriate prescribing in NHs have been tested. Pharmacist-led medication review, probably the most investigated intervention, has been shown to have some impact on PIP.[12] A positive impact has also been demonstrated for educational approaches and computerized clinical decision support systems.[13–16]

So far, most interventions have focused on a single component. As several authors have suggested, a multifaceted approach seems preferable.[13,14,17,18] Because healthcare professionals (HCPs) in NHs may not be sufficiently trained in pharmacotherapy for older people, it is further recommended to involve an interdisciplinary team and to integrate an educational aspect into every intervention.[13,14]

NH settings and context can differ between countries. Thus, policy approaches for optimizing medication use in NHs can vary. In 2013, a national call was launched in Belgium to perform a quality improvement project, aimed at evaluating the effect of interdisciplinary collaboration on the appropriateness of use of medications by NH residents and developing recommendations for policy makers (COME-ON study: Collaborative approach to Optimize Medication use for Older people in Nursing Homes).

The aim of this report is to describe the impact of a complex multifaceted intervention, developed in the COME-ON study, on the appropriateness of prescribing for NH residents.

Methods

Design Overview

A multicenter, nonblinded, cluster-randomized controlled trial was developed in accordance with the extension of the Consolidated Standards of Reporting Trials (CONSORT) statement to cluster randomized controlled trials.[19] The study was approved by the Ethics Committee (s57145, ML11035) and the Privacy Commission (14/095; SCSZ/14/084/174). Written informed consent was obtained from NH residents or their representatives (after randomization). The study protocol has been published.[20]

Setting

The study was performed in Belgian NHs, which are long-term care facilities for older adults. In Belgium, NH residents can choose their general practitioner (GP). The GP has total freedom in the choice of therapeutic strategies. Each NH is obliged to appoint one GP as coordinating physician, who is responsible for training, coordination of quality initiatives, etc. The role of the pharmacist is often restricted to the supply of medication. So far, medication review has not been formally implemented.

Recruitment and Randomization

Sixty-three NHs that applied to participate in the study were considered eligible for randomization. NH residents could participate if they were aged 65 years or over and under the care of a participating GP. Residents receiving palliative care (as evaluated by the treating GP) or in subacute care/rehabilitation were excluded. Recruitment of NH residents was performed between January and April 2015.

Randomization was performed at the NH level. The allocation was stratified according to province, previous experience with case conferencing, and type of pharmacy (hospital or community pharmacy).

Each GP only had patients included in either the intervention or the control group. Blinding of participating NHs and HCPs was not possible. Sample size estimations were conducted beforehand.[20]

Intervention

The Medical Research Council guidelines for developing and evaluating complex interventions were followed in developing the study.[21] The complex intervention consisted of 3 interacting components: a blended training program, local interdisciplinary meetings, and interdisciplinary case conferences (ICC). ICCs involving the GP, pharmacist, and nurse were considered the key component and consisted of structured and repeated interdisciplinary face-to-face medication reviews (every 4 months, ie, 3 times over a 12-month period). During each ICC, all medications of the NH residents were critically reviewed and interventions to optimize the resident's medication use were discussed. Local interdisciplinary meetings were organized to discuss the rational use of a single medication class at the NH level. The training for HCPs consisted of both e-learning and (interdisciplinary) face-to-face workshops, including topics on pharmacotherapy for older people and medication review.

The intervention was carried out from May 2015 to June 2016. The control NHs delivered usual care.

Data Collection

Administrative data, clinical data, comorbidities, medication data, laboratory values, and data regarding healthcare use were recorded by the HCPs involved. Data collection was performed at 3 time points (baseline, middle, and end of study, in months 1, 8, and 15, respectively) and during each ICC (intervention group); data were collected through a secure web application. Financial incentives were provided for each HCP after each time point when data were completed. Baseline data collection started in April 2015 and final data were collected in June 2016.

Outcome Measures

The primary outcome measure related to the appropriateness of prescribing at the resident level and was considered successful when at least 1 PIM or PPO that was present at baseline had been solved at the end of the study (outcome A), and when there were no new PIMs or PPOs at the end of study compared with baseline (outcome B). For residents with no PIM or PPO at baseline (outcome A not applicable), the intervention was considered successful if outcome B was achieved. Additional analyses were conducted to investigate the effect of the intervention in the middle of the study (month 8 versus baseline). PIP was measured using the STOPP-START criteria and the Beers' criteria through an algorithm that automatically detected PIMs and PPOs in the research database.[22–24] This algorithm was not available to HCPs when preparing or implementing ICCs.

Secondary outcomes at the resident level included clinical outcomes (mortality and healthcare use), medication use, prevalence of PIM and PPO per criterion, and outcomes of ICCs (median number of ICC per NH resident, median number of drug-related problems (DRPs) per NH resident, cause and type of identified DRPs and interventions, implementation status, and drugs involved). The results of the cost analysis are not presented in this report.

Table 1
Baseline Characteristics of NHs and NH Residents

Characteristics	Intervention Group	Control Group
NHs, n	24	30
Median number of beds (IQR)	121 (106–163)	108 (82–144)
Type of institution, n (%)		
Private nonprofit	16 (66.7%)	19 (63.3%)
Private for-profit	1 (4.2%)	5 (16.7%)
Public (nonprofit)	7 (29.2%)	6 (20.0%)
Type of supplying pharmacy, n (%)		
Community pharmacy	23 (95.8%)	28 (93.3%)
Hospital pharmacy	1 (4.2%)	2 (6.7%)
Experience with ICC, n (%)	9 (37.5%)	11 (36.7%)
Nursing home residents, n	847	957
Median age (IQR)	87 (82–92)	88 (83–92)
Female, n (%)	590 (69.7%)	682 (71.3%)
Nursing home residents with complete data*, n	791	716
Median number of NH residents per NH for whom baseline data were complete	35 (32.35–35)	26 (16.5–31.5)
Median age (IQR)	87 (82–91)	87 (83–91)
Female, n (%)	553 (69.9%)	526 (73.4%)
Median number of years since institutionalization in nursing home (IQR)	2 (1–5)	3 (1–5)
Median Katz score (IQR)	17 (13–21)	17 (13–21)
Dependency categories (Katz scale), n (%)		
O = cognitively fit and physically independent	83 (10.5%)	62 (8.7%)
A = minor physical dependency, no dementia, or dementia and physically independent	86 (10.9%)	114 (15.9%)
B = major physical dependency, no dementia, or dementia and minor physical dependency	220 (27.8%)	197 (27.5%)
C = full physical dependency, no dementia	97 (12.3%)	93 (13.0%)
D = diagnosis of dementia established by a neurologist, geriatrician, or psychiatrist	33 (4.2%)	4 (0.6%)
Cd = full dependency and dementia	272 (34.4%)	246 (34.4%)
Median comorbidity score (CIRS-G) (IQR)	25 (21–29)	24 (21–28)
Three most prevalent comorbidities		
Hypertension, n (%)	443 (56.0%)	402 (56.1%)
Dementia/dementia syndrome/cognitive impairment, n (%)	471 (59.5%)	388 (54.2%)
Osteoarthritis, n (%)	501 (63.3%)	474 (66.2%)
Median MMSE score (IQR)	18 (13–24)	19 (13–24)
Median eGFR according to MDRD (mL/min/1.73 m^2) (IQR)	60 (48–75)	60 (48–76)
Median number of medications at baseline (IQR)	9 (6–12)	9 (6–11)
Categories for number of medications at baseline		
0–4	95 (12.0%)	92 (12.8%)
5–9	328 (41.5%)	308 (43.0%)
≥10	368 (46.5%)	316 (44.1%)
Median number of PIMs (Beers and STOPP) at baseline (IQR)	2 (1–4)	2 (1–4)
Median number of PPOs (START) at baseline (IQR)	2 (1–3)	2 (1–3)

CIRS-G, Cumulative Illness Rating Scale–Geriatric; eGFR, estimated glomerular filtration rate; HCP, healthcare professional; ICC, interdisciplinary case conferences; MDRD, modified diet renal disease; MMSE, Mini-Mental State examination; STOPP, Screening Tool of Older Person's Prescriptions; START, Screening Tool to Alert doctors to Right Treatment.

*Complete data means that the GP, the pharmacist, and the nurses had filled in the electronic data collection forms on comorbidities, laboratory values, medications, and clinical data at baseline. However, they were given the possibility of answering 'I don't know' (eg, if a specific diagnosis or lab value was not available for this NH resident), which explains why there are different numbers of missing data for some characteristics. The number of NH residents with missing data were age of NH resident: n = 15; Katz score: n = 188; MMSE score: n = 505; eGFR: n = 589.

A detailed process evaluation was performed and will be described in a separate report.

Statistical Analysis

Primary outcome

A binary logistic mixed-effects model was applied. A 3-level mixed-effects model was used to account for clustering of the data: NH residents were nested within GPs and GPs in their turn were nested within NHs. The 3 stratification variables used to allocate NHs to intervention or control arm were included as covariates. The analysis was performed by original assigned groups.

The database contained a high proportion of missing data (Supplementary Table 1). To avoid analyzing only complete cases, which entails a risk of biased estimates of the intervention effect if the missing data is not random,[25] a multiple imputation strategy on all 1804 NH residents was followed for the primary outcome. Multiple imputation was performed using the fully conditional specification approach.[26] In this approach, for each variable with a missing value, a regression model is specified using all the other predictors and outcome variables as covariates. Depending on the variable, a linear regression or binary logistic regression model was used. The process was iterated (1 iteration consists of 1 cycle through all variables) until convergence with the multivariate distribution was obtained. Ten complete datasets were created. The mixed-effects model was applied to each of the 10 datasets. In a pooling phase, the estimates for the 10 datasets were integrated into 1 estimate for each effect using the Rubin's rule.[27] The covariates needed for the imputation were initially selected based on clinical grounds. A definitive selection of the covariates was done by means of a random forest analysis. In this analysis, all potential covariates were used to predict primary outcome A and B separately. Afterward, the covariates with a variance importance score of ≥5 were selected to be used in the multiple imputation model (Supplementary Table 2). In addition to these covariates, the treatment indicator variable was included in the imputation model.

Secondary outcomes

Analyses of healthcare use were conducted on the subsample of NH residents for whom the required data were fully completed (n = 985). For mortality, all NH residents were taken into account (n = 1804), and for medication use, the NH residents with full data on medication were included in the analyses (n = 1139). Depending on

Table 2
Odds Ratios for a Successful Primary Outcome A+B, Outcome A, and Outcome B for Comparison of End Data vs Baseline (Primary Outcome) and for Comparison of Middle Data vs Baseline, Obtained From 3-Level Logistic Regression Models With the Stratification Variables Added as Covariates (Including all 1804 NH Residents)

Variables	Odds Ratio (95% CI)	*P* value
Comparison end data vs baseline		
Primary outcome (outcome A+B)		
Intervention effect	1.479 (1.062–2.059)	.021*
Outcome A		
Intervention effect	2.666 (1.784–3.983)	<.001*
Outcome B		
Intervention effect	0.664 (0.458–0.961)	.030*
Comparison middle data vs. baseline		
Outcome A+B		
Intervention effect	2.194 (1.49–3.23)	<.001*
Outcome A		
Intervention effect	3.311 (2.075–5.282)	<.001*
Outcome B		
Intervention effect	0.561 (0.383–0.821)	.003*

Outcome A = when at least 1 PIM or PPO that was present at baseline had been solved at the end of the study; outcome B = when there was no new PIM or PPO at the end of the study compared with baseline; outcome A+B = when at least 1 PIM or PPO that was present at baseline had been solved at the end of the study and when there was no new PIM or PPO at the end of the study compared with baseline.
*Significant: $P < .05$.

the type of data (binary, counts, continuous), a logistic regression model, a regression model for count data (Poisson or negative binomial), or a linear regression model on log-transformed data (ie, duration of hospitalization) was used. Random effects were used to take clustering into account. Stratification variables and other possible confounding variables (age, sex, time since institutionalization, Katz score, palliative status, number of medications/PIMs/PPOs at baseline, and comorbidity score (Cumulative Illness Rating Scale—Geriatric) were added in the specific regression model.

The difference between the use of specific medication classes (defined as the number of NH residents using ≥1 drug from these classes, based on Anatomic Therapeutic Chemical level 3[28]) between baseline and end of study was compared using the McNemar test.

Analyses regarding the prevalence of PIMs and PPOs per criterion were performed on the subsample of NH residents for whom data on medication and PIMs or PPOs were complete at baseline and the end of study (n = 666 for PIMs and n = 371 for PPOs).

Analyses of outcomes of ICCs were conducted on those NH residents from the intervention group for which at least 1 ICC was registered (n = 681). *P* values of <.05 were considered statistically significant.

Analyses were done with SPSS Statistics for Windows v 24.0 (IBM Corp., Armonk, NY) and R software v 3.3.3 (2017-03-06; R Foundation for Statistically Computing, Vienna, Austria) in Rstudio.

Results

Baseline Characteristics of NHs, NH Residents, and HCPs

Supplementary Figure 1 shows the flow of participants through our trial. Of the 63 NHs selected, 54 participated. In total, 1804 NH residents were included. For 1507 NH residents, full data (ie, clinical, medication, comorbidities, and laboratory values) were available at baseline. Overall, baseline characteristics of NHs and NH residents were similar between groups (Table 1). In total, 701 HCPs participated (55 coordinating physicians, 378 GPs, 85 pharmacists, and 183 nurses). The majority were male (n = 379/701; 54.1%). Their median age was 51 [interquartile range (IQR) 40.3-58.8].

Primary Outcome

Table 2 presents the data on the primary outcome. We found the intervention to have a significant positive effect on the primary outcome measure (A+B) in a comparison of both end ($P = .021$) and middle ($P < .001$) data and baseline. The intervention had a positive effect on outcome A. The effect on outcome B was negative. The number needed to treat for outcome A+B to be considered successful at end of study (calculated using data after imputation) was 19.

Secondary Outcomes

Clinical outcomes are presented in Supplementary Table 3. They did not significantly differ between groups, except mortality rate, which was significantly higher in the intervention group ($P = .015$), and the median duration of hospitalization, which was significantly longer in the control group. No significant difference in the overall number of medications used at the end of study was observed. The median number of medications did not change over time in either group.

Use of specific medication classes

The most frequently used medication classes at baseline for both groups (used in >15% of NH residents) for which significant changes over time were observed within groups are shown in Table 3.

Significant decreases in the consumption of antithrombotic agents, drugs for peptic ulcer and GERD (Gastro Esophageal Reflux Disease)/GORD (Gastro Oesophageal Reflux Disiease), hypnotics, and sedatives were obtained in the intervention group but not in the control group. The use of lipid modifying agents decreased in both groups, but much more in the intervention group. In the intervention group, a significant increase was seen in the use of vitamin A and D. The use of drugs for constipation significantly increased in both groups. In the control group, a significant increase in the use of pain medication (both opioids and other analgesics) was observed.

Prevalence of PIMs and PPOs per criterion

The 10 most prevalent PIP criteria are presented in Tables 4 and 5. Regarding PIMs, most criteria relate to the use of psychotropics. The intervention group was observed to have a slightly greater decrease in prevalence over time for the benzodiazepines. Underuse of vitamin D substantially decreased in the intervention group.

Case conferences

Altogether, 1675 ICCs took place, with a median of 3 ICCs (IQR = 2–3) per NH resident. The median duration of the ICC was 15 minutes. In total, 3508 DRPs were registered, with a median of 4 DRPs per NH resident (IQR = 2–7). The most frequently registered cause was “no indication for the drug” (810/3508; 23.1%). “Discontinuation or tapering medication” was the most frequently registered intervention (1146/3508; 32.7%). Based on the available data on implementation, most interventions were implemented as planned (1171/1407; 83.2%). The drug classes most often involved in DRPs were drugs for the central nervous system (mainly benzodiazepines), alimentary tract and metabolism (mainly proton pump inhibitors), and cardiovascular system (proportions of 40.8%, 30.4%, and 17.0%, respectively). Additional data on ICCs will be reported in a separate report about the process evaluation.

Discussion

In this cluster-controlled trial, involving a complex multifaceted intervention, we observed that the intervention had a significant positive effect on resolving existing PIMs and PPOs but a negative effect on preventing new PIMs and PPOs. The overall effect on

Table 3
Most Frequently Used Medication Classes at Baseline (>15% of NH Residents; ATC-Level 3) for Which a Significant Change Was Observed in Intervention and/or Control Groups Between Baseline and End of Study

Medication Class Users (ATC Level 3)	Intervention Group n = 508			Control Group n = 631		
	Residents Baseline	Residents End	*P* value*	Residents Baseline	Residents End	*P* value*
Drugs for peptic ulcer and gastro-oesophageal reflux disease (GERD/GORD) (A02B)	235 (46.3%)	204 (40.2%)	<.001†	278 (44.1%)	278 (44.1%)	.999
Drugs for constipation (A06A)	275 (54.1%)	298 (58.7%)	.000†	327 (51.8%)	349 (55.3%)	.000†
Vitamin A and D, incl combinations (A11C)	153 (30.1%)	255 (50.2%)	.000†	224 (35.5%)	222 (35.2%)	.5
Calcium (A12A)	126 (24.8%)	123 (24.2%)	.250	142 (22.5%)	123 (19.5%)	.000†
Antithrombotic agents (B01A)	283 (55.7%)	260 (51.2%)	.003†	365 (57.8%)	363 (57.5%)	.777
High-ceiling diuretics (C03C)	140 (27.6%)	144 (28.3%)	.125	169 (26.8%)	175 (27.7%)	.031†
Beta-blocking agents (C07A)	170 (33.5%)	164 (32.1%)	.031†	246 (39.0%)	234 (37.1%)	.000†
Selective calcium channel blockers with mainly vascular effect (C08C)	84 (16.5%)	79 (15.6%)	.063	112 (17.7%)	98 (15.5%)	.000†
Lipid modifying agents (C10A)	122 (24.0%)	73 (14.4%)	<.001†	128 (20.3%)	114 (18.1%)	.004†
Opioids (N02A)	91 (17.9%)	95 (18.7%)	.586	104 (16.5%)	123 (19.5%)	.003†
Other analgesics and antipyretics (N02B)	263 (51.8%)	279 (54.9%)	.113	271 (42.9%)	290 (46.0%)	.008†
Anxiolytics (N05B)	179 (35.2%)	171 (33.7%)	.267	235 (37.2%)	219 (34.7%)	.036†
Hypnotics and sedatives (N05C)	156 (30.7%)	140 (27.6%)	.016†	163 (25.8%)	165 (26.1%)	.763

ATC, Anatomic Therapeutic Chemical.
Medication includes chronic, acute, and as needed medications; compounded medications are excluded.
*The differences in use of specific medication classes (defined as the number of NH residents who used at least one drug from these classes, based on ATC level 3) between baseline and end of study within the intervention and control groups was compared using the McNemar test.
†Significant: $P < .05$.

Table 4
The 10 Most Prevalent PIP Criteria According to STOPP v2 and the AGS 2015 Beers Criteria at Baseline

Criterion	Intervention Group n = 317		Control Group n = 349	
	Residents Baseline	Residents End	Residents Baseline	Residents End
According to STOPP v2				
K1 – Benzodiazepines	172 (54.3%)	158 (49.8%)	195 (55.9%)	189 (54.2%)
D5 – Benzodiazepines for ≥4 wk	171 (53.9%)	152 (47.9%)	187 (53.6%)	179 (51.3%)
K2 – Neuroleptic drugs	118 (37.2%)	116 (36.6%)	117 (33.5%)	112 (32.1%)
I1 – Antimuscarinic drugs for overactive bladder syndrome with concurrent dementia or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism	46 (14.5%)	44 (13.9%)	45 (12.9%)	52 (14.9%)
D9 – Neuroleptic antipsychotic in patients with behavioral and psychological symptoms of dementia (BPSD), unless symptoms are severe and other treatments have failed	41 (12.9%)	52 (16.4%)	58 (16.6%)	54 (15.5%)
D8 – Anticholinergics/antimuscarinics in patients with delirium or dementia	38 (12.0%)	39 (12.3%)	38 (10.9%)	45 (12.9%)
F3 – Drugs likely to cause constipation (eg, antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminum antacids) in patients with chronic constipation where nonconstipating alternatives are appropriate	35 (11.0%)	43 (13.6%)	42 (12.0%)	46 (13.2%)
K4 – Hypnotic z-drugs	33 (10.4%)	26 (8.2%)	34 (9.7%)	29 (8.3%)
M1 – Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties	30 (9.5%)	18 (5.7%)	27 (7.7%)	27 (7.7%)
B9 – Loop diuretic for treatment of hypertension with concurrent urinary incontinence	17 (5.4%)	16 (5.0%)	12 (3.4%)	16 (4.6%)
According to the AGS 2015 Beers criteria				
T3_5_B Dementia or cognitive impairment. Anticholinergics, benzodiazepines, H2-receptor antagonists, nonbenzodiazepine, benzodiazepine receptor agonist hypnotics, eszopiclone, zolpidem, zaleplon, antipsychotics, chronic and as-needed use	216 (68.1%)	205 (64.7%)	231 (66.2%)	226 (64.8%)
T3_6_B History of falls or fractures – anticonvulsants, antipsychotics, benzodiazepines, nonbenzodiazepine, benzodiazepine receptor agonist hypnotics, eszopiclone, zaleplon, zolpidem, TCAs, SSRIs, opioids	175 (55.2%)	165 (52.1%)	246 (70.5%)	230 (65.9%)
T2_19_B Benzodiazepines short- and intermediate-acting	148 (46.7%)	130 (41.0%)	159 (45.6%)	157 (45.0%)
T2_17_B Antipsychotics, first (conventional) and second (atypical) generation	97 (30.6%)	92 (29.0%)	107 (30.7%)	97 (27.8%)
T2_32_B Proton-pump inhibitors: Avoid scheduled use for >8 wk unless for high-risk patients (eg, oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett's esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (eg, due to failure of drug discontinuation trail or H2 blockers)	93 (29.3%)	77 (24.3%)	105 (30.1%)	105 (30.1%)
T5_5_B Benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics + ≥2 other CNS-active drugs	87 (27.4%)	79 (24.9%)	92 (26.4%)	108 (30.9%)
T5_4_B Antipsychotics + ≥2 other CNS-active drugs	66 (20.8%)	55 (17.4%)	63 (18.1%)	64 (18.3%)
T5_9_B Opioid receptor agonist analgesics + ≥ 2 other CNS-active drugs	37 (11.7%)	35 (11.0%)	48 (13.8%)	56 (16.0%)
T2_21_B Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics, eszopiclone, zolpidem, zaleplon	33 (10.4%)	26 (8.2%)	34 (9.7%)	29 (8.3%)
T5_3_B Antidepressants (ie, TCAs and SSRIs) + ≥2 other CNS-active drugs	33 (10.4%)	34 (10.7%)	39 (11.2%)	41 (11.7%)

Table 5
The 10 Most Prevalent Potential Prescribing Omissions Criteria According to START v 2

Criterion	Intervention Group n = 187		Control Group N = 184	
	Residents Baseline	Residents End	Residents Baseline	Residents End
E5 - Vitamin D supplement in older people who are housebound, experiencing falls, or with osteopenia (bone mineral density T score is >-1.0 but <-2.5 in multiple sites)	99 (52.9%)	50 (26.7%)	90 (48.9%)	89 (48.4%)
A3 – Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral, or peripheral vascular disease	41 (21.9%)	50 (26.7%)	26 (14.1%)	28 (15.2%)
G3 – Topical vaginal estrogen or vaginal estrogen pessary for symptomatic atrophic vaginitis	39 (20.9%)	41 (21.9%)	38 (20.7%)	40 (21.7%)
E4 – Bone antiresorptive or anabolic therapy (eg, bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacologic or clinical status contraindication exists (bone mineral density T scores ->2.5 in multiple sites) and/or previous history of fragility fracture(s)	37 (19.8%)	46 (24.6%)	50 (27.2%)	54 (29.3%)
E3 – Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (bone mineral density T-scores more than −2.5 in multiple sites)	24 (12.8%)	32 (17.1%)	34 (18.5%)	45 (24.5%)
A5 – Statin therapy with documented history of coronary, cerebral, or peripheral vascular disease, unless the patient's status is end-of-life or age is >85 y	23 (12.3%)	26 (13.9%)	13 (7.1%)	11 (6.0%)
A6 – ACE inhibitor with systolic heart failure and/or documented coronary artery disease	22 (11.8%)	25 (13.4%)	21 (11.4%)	19 (10.3%)
A7 – Beta-blocker with ischemic heart disease	7 (3.7%)	6 (3.2%)	7 (3.8%)	7 (3.8%)
B1 - Regular inhaled beta 2 agonist or antimuscarinic bronchodilator (eg, ipratropium, tiotropium) for mild to moderate asthma or COPD	7 (3.7%)	8 (4.3%)	5 (2.7%)	7 (3.8%)
C3 – Acetylcholinesterase inhibitor (eg, donepezil, rivastigmine, galantamine) for mild/moderate Alzheimer's, dementia, or Lewy body dementia (rivastigmine)	7 (3.7%)	6 (3.2%)	16 (8.7%)	6 (3.3%)

ACE, angiotensin converting enzyme; BPSD behavioral and psychological symptoms of dementia; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; NSAID non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

appropriateness of prescribing was positive. There was no significant difference between groups on secondary outcome measures, except for a negative effect on mortality and a positive effect on duration of hospital stay.

The positive effect is consistent with the impact observed in other studies that have aimed to improve appropriate prescribing for older people, though in different environments. Recently, in a cluster RCT in Dutch NHs involving a multidisciplinary multistep medication review, a significant impact on successful discontinuation of ≥1 inappropriate medication was observed.[29] In the OPTI-SCRIPT (Optimizing Prescribing for Older People in Primary Care) study (multifaceted intervention study in primary care), the intervention had a significant positive effect on PIP.[30] However, directly comparing studies is difficult. Only 1 study (Desborough et al) seems comparable to ours (in terms of intervention, setting, and outcomes), but the results have not yet been published.[31]

The results obtained in our study were observed in a real-life context (ie, with HCPs involved in the care of NH residents). Unlike the DIM-NHR (Discontinuing Inappropriate Medication in Nursing Home Residents) study, in which an external pharmacist appointed to conduct medication review in NHs was involved, the pharmacists in the COME-ON study were the pharmacists supplying medication. The former might have been more experienced than our community pharmacists. Our data also suggest that solving an existing PIM or PPO is easier than preventing a new one. Many modifications were proposed and implemented during the ICCs and new PIMs and PPOs may have been introduced. Moreover, the outcomes of the ICCs suggest that our algorithm did not capture all modifications (eg, dose reduction of benzodiazepines was not considered a resolved PIM, although tapering is a relevant intervention). Although many DRPs relate to STOPP/START items, the detailed analysis of the DRP data (problems and interventions) shows that individual aspects of medication use were taken into account during ICCs and, hence, that DRPs go beyond STOPP/START. The impact on prevalence of PIMs and PPOs over time was limited. For some, HCPs may have argued that they were not relevant or that solving them was not possible, whereas others may not even have been detected.

Comparing the primary outcome A+B (end vs baseline) with the middle data suggests that the effect decreases over time. The size of the effect, however, remained significant at end of study, which is encouraging. This is similar to what Frankenthal et al reported on the long-term outcomes of a medication intervention based on STOPP/START.[32] They found a significant rise in PIMs and PPOs in the intervention group between 12 and 24 months, but the prevalence of PIMs remained significantly lower than in the control group.

Selection of appropriate outcome measures was not evident and may be subject to discussion. Recently, 2 core outcome sets (COS) have been developed, defining outcomes that should always be measured in trials aimed at optimizing prescribing for older people.[33,34] In both COS, measures relative to appropriateness of prescribing (in line with our primary outcome measure) were included. Healthcare utilization outcomes were also included but somewhat differed. Number of medicines and mortality were only included in 1 of the COS[34]; they were not withheld in the COS that was developed in co-creation with a large number of older persons.[33]

No substantial effect on overall medication use was observed, but reducing medication was not a specific aim as such. Furthermore, we found a significant (greater) decrease and increase in prevalence of use for several classes of medications in the intervention group. These classes include medications known to be frequently overused or underused and which were addressed during the training and local interdisciplinary meetings (drugs for peptic ulcer, hypnotics and sedatives, lipid-modifying agents, and vitamin D).

Data on clinical outcomes must be interpreted with great caution because they were calculated on a subset of residents for whom the respective data were complete. Moreover, HCPs self-reported, data could not be retrieved from national databases, there was no adjudication of clinical events to identify if they were possibly drug-related and there was no adjustment for additional (unknown) factors. For mortality, the cause of death was not known and the relationship with the intervention cannot be evaluated. Moreover, place of death was not registered and correlation with length of stay could not be

investigated. As indicated by the divergent COS, death is also not the most important outcome when it comes to evaluating the impact of medication review.[33] The limited impact we observed is in line with the conclusion of Alldred et al.[7] Like the OPTI-SCRIPT study on patient-reported outcomes, the DIM-NHR study also showed no difference between the groups in terms of clinical outcomes. This might be attributable to our choice of clinical outcomes. The recent published core outcome set suggests it would have been more important to assess drug-related admissions, which was not foreseen in this study.[33]

Strengths and Limitations

This study has several strengths, including its design, the multifaceted approach, and the large sample size. The primary outcome was based on a criterion-specific change over time. We believe this is an appropriate choice for measuring the effect, as it provides more detailed information than measuring the evolution in overall number of PIMs/PPOs. Moreover, we addressed all 3 categories of PIP.

Some limitations should also be acknowledged. Explicit tools were incorporated into our algorithm to detect PIMs and PPOs. These tools do not take individual aspects into consideration, nor cover all aspects of appropriateness of prescribing.[12] Furthermore, these criteria are not specific to NH residents. Since we started the study, criteria that better apply to older people in NH settings have been developed.[35–37] We plan to use these criteria in post-hoc analyses. In addition, selection bias might have occurred because only NHs that applied freely were included. Moreover, only NH residents being treated by GPs who were willing to participate in the study were included. From the process evaluation, we learned that these GPs were among the “most open". This could affect efforts to generalize our findings. Finally, the relatively high number of missing data shows how difficult research is in this setting. We performed data imputation for the primary outcome but were not able to apply this technique for the secondary outcomes. In the future, improved availability and access to electronic health data should help to overcome this barrier.

Conclusions and Implications

The complex multifaceted intervention conducted in the COME-ON study has been shown to be effective in improving rational prescribing for NH residents. This result, along with the data from the process evaluation, could serve as a basis for recommendations for wider implementation of interdisciplinary medication review to optimize medication use in NHs.

Acknowledgments

We thank Dr Koen Vanbrabant and Dr Steffen Fieuws for their help with the statistical analyses. We are very grateful to Robert Houdart for his contribution in the development of the web application and his technical support. Moreover, Anne-Elisabeth Petit’s help with the analyses of medication use was greatly appreciated. We also thank the nursing homes, healthcare professionals, and residents for their participation in the study, as well as all members of the consortium for their contribution to the COME-ON study: Benoit Boland, Olivia Dalleur, Anja Declercq, Jean-Marie Degryse, Valérie Lacour, Steven Simoens, Niko Speybroeck, and Kris Vanhaecht.

Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2019.06.006.

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