Annals of Internal Medicine ORIGINAL RESEARCH

Discontinuing Inappropriate Medication Use in Nursing Home Residents

A Cluster Randomized Controlled Trial

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Background: Inappropriate prescribing is a well-known clinical problem in nursing home residents, but few interventions have focused on reducing inappropriate medication use.

Objective: To examine successful discontinuation of inappropriate medication use and to improve prescribing in nursing home residents.

Design: Pragmatic cluster randomized controlled trial, with clustering by elder care physicians and their wards. (ClinicalTrials.gov: NCT01876095)

Setting: 59 Dutch nursing home wards for long-term care.

Patients: Residents with a life expectancy greater than 4 weeks who consented to treatment with medication.

Intervention: Multidisciplinary Multistep Medication Review (3MR) consisting of an assessment of the patient perspective, medical history, critical appraisal of medications, a meeting between the treating elder care physician and the pharmacist, and implementation of medication changes.

Measurements: Successful discontinuation of use of at least 1 inappropriate drug (that is, without relapse or severe withdrawal symptoms) and clinical outcomes (neuropsychiatric symptoms, cognitive function, and quality of life) after 4 months of follow-up.

Results: Nineteen elder care physicians (33 wards) performed the 3MR, and 16 elder care physicians (26 wards) followed standard procedures. A total of 426 nursing home residents (233 in the intervention group and 193 in the control group) were followed for an average of 144 days (SD, 21). In an analysis of all participants, use of at least 1 inappropriate medication was successfully discontinued for 91 (39.1%) residents in the intervention group versus 57 (29.5%) in the control group (adjusted relative risk, 1.37 [95% CI, 1.02 to 1.75]). Clinical outcomes did not deteriorate between baseline and follow-up.

Limitations: The 3MR was done only once. Some withdrawal symptoms or relapses may have been missed.

Conclusion: The 3MR is effective in discontinuing inappropriate medication use in frail nursing home residents without a decline in their well-being.

Primary Funding Source: Netherlands Organisation for Health Research and Development.

Ann Intern Med. 2017;167:609-617. doi:10.7326/M16-2729 **Annals.org**
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This article was published at Annals.org on 10 October 2017.

Polypharmacy, often defined as coincident prescribing of at least 5 long-term medications, is associated with an increased risk for inappropriate prescribing. As many as 40% of nursing home residents may receive 1 or more inappropriate drugs (1), a rate similar to that among community-dwelling older persons (2). In nursing home residents, inappropriate prescribing has been shown to be associated with adverse events (3) and hospitalizations (4). Inappropriate prescribing of antihypertensives, benzodiazepines, and the atypical antipsychotic quetiapine has been associated with increased fall risk in community-dwelling older persons (5), loss of physical function in community-dwelling older women (6), and an increase in cognitive decline in nursing home residents (7), respectively. In addition to overprescribing, inappropriate prescribing may also manifest as underprescribing (the omission of appropriate medication). Underprescribing of oral anticoagulants among nursing home residents has been reported (8).

Deprescribing has been defined as "the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" (9). Studies targeting discontinuation of use of specific medications have shown mixed results. Bergh and colleagues (10) found a worsening of depressive symptoms after discontinuation of antidepressant use but concluded that this worsening was in the subclinical range. A systematic review showed that many patients remained normotensive after withdrawal of antihypertensives, although proportions ranged from 20% to 85% across studies (11). Furthermore, conflicting results were found for discontinuation of antipsychotic use and risk for relapse of neuropsychiatric symptoms (12, 13).

Multidisciplinary systematic medication reviews done by physicians and pharmacists working together are aimed at improving prescribing in patients with polypharmacy, but findings about their effectiveness have been equivocal (14–18). Negative findings may have been due to inclusion of inappropriate outcomes (17) and heterogeneity of interventions. Medication re-

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views were performed by a multidisciplinary team of physicians and pharmacists in some studies but were done by a single health professional in others (19). More extensive intervention studies using well-defined pharmacologic outcome measures and proximal outcomes indicative of patients' well-being are needed (18). Moreover, evidence on the effectiveness of multidisciplinary systematic medication reviews is limited for nursing home residents, a particularly vulnerable population.

Accordingly, the aim of this study was to assess whether multidisciplinary systematic medication reviews increase successful discontinuation of inappropriate medication use, improve prescribing in other respects, and improve clinical outcomes in nursing home residents.

METHODS

Design Overview

We conducted the DIM-NHR (Discontinuing Inappropriate Medication in Nursing Home Residents) study, a pragmatic cluster randomized controlled trial. Clusters of elder care physicians and their wards with residents from the 3 northern provinces of the Netherlands were randomly allocated to the intervention or control group in a 1:1 ratio. Participants were recruited between June 2014 and December 2015, and follow-up was completed in April 2016. The Medical Ethical Committee of the University Medical Center Groningen approved the study (protocol number NL48091.042.14). Written informed consent was requested from residents in wards for disabling conditions if they were deemed capable by the nursing staff. Informed consent from a legal representative was requested for residents who were not capable of providing informed consent and for those from dementia special care units. The study's methods have been published (20). The original trial protocol and a summary of changes to it are provided in the Supplement (available at Annals.org).

Setting and Participants

We screened nursing home wards, elder care physicians, and nursing home residents for eligibility. Nursing home wards were eligible if they were dementia special care units or if they provided care for residents with disabling conditions. We included long-term care wards to reduce loss of participants to follow-up. Nursing home wards were excluded if they primarily cared for atypical patients (for example, those with lifelong psychiatric disorder or intellectual disability), if they participated in other research aimed at improving drug prescribing within the previous 12 months, or if medication reviews had been done within 6 months before the beginning of recruitment. Unlike in many other countries, where different nursing home residents have different primary care physicians, in the Netherlands, specialized elder care physicians are based in the nursing home. We recruited pharmacists and elder care physicians who were committed to performing the medication reviews. Elder care physicians were ineligible if they previously received or were about to receive recertification for systematic medication reviews. Nursing home residents were included if they had a life expectancy greater than 4 weeks and were deemed ineligible if they declined treatment with medication or at the discretion of nursing staff (for example, because of a difficult relationship between nursing home staff and family members).

Randomization and Intervention

Cluster randomization was performed at the level of the elder care physicians and the wards they were responsible for in order to minimize contamination that might occur if individual nursing home residents who shared the same elder care physician were randomly assigned to different groups. Elder care physicians and their wards were first matched on relevant characteristics, including supplying pharmacy, health care organization, and ward type (for example, wards for residents with dementia vs. residents with disabling conditions and number of residents in the ward). For each matched pair of physicians, one was randomly assigned to the intervention group and the other to the control group. The random assignment was generated using the random variable function in SPSS software and was done by a researcher who was not involved in data collection. Because physicians and pharmacists implemented the intervention, they were not blinded to the allocation of wards to the intervention or control group. Other nursing home staff, nursing home residents, and assessors of outcomes were not informed about the treatment allocation.

The intervention consisted of a single Multidisciplinary Multistep Medication Review (3MR) (Table 1) that was done by the treating elder care physicians in collaboration with hospital pharmacists or pharmacists appointed to conduct medication reviews in nursing homes. Participating elder care physicians and pharmacists received brief training about the 3MR before performing it. Adherence to the 3MR was checked by confirming with the pharmacists whether steps 1 to 3 had been completed and confirming with the physicians whether step 4 had been completed. The control condition consisted of usual care, including medication safety monitoring and ad hoc medication reviews for individual residents when clinically indicated. These reviews differed in quality and frequency from the standardized 3MRs performed in the intervention group.

Outcomes and Follow-up

Primary and secondary outcome measures were collected at baseline and after 4 months. This follow-up was chosen because it allowed for consolidation of medication changes while also preventing excessive loss to follow-up owing to substantial mortality risk among these frail patients.

The primary outcome was the proportion of residents who successfully discontinued use of at least 1 inappropriate medication (that is, without relapse symptoms or severe withdrawal effects) after 4 months of follow-up. Pharmacy and medical interns reviewed

all physician notes in each resident's medical chart between baseline and follow-up to detect potential withdrawal or relapse symptoms. Medications that had to be tapered gradually (such as narcotics or steroids) because of the potential for severe withdrawal effects were not excluded from the intervention and were included in the count of successful discontinuations. A switch of an inappropriate medication to another medication in the same Anatomical Therapeutic Chemical (ATC) group was not considered a successful discontinuation. Medications were excluded if they were prescribed temporarily (for example, antibiotics, dermatologic agents, or as-needed medications).

Secondary pharmacologic outcomes were the number of residents for whom at least 1 underprescribed medication (according to the START [Screening Tool to Alert doctors to Right Treatment] criteria [21]) was initiated between baseline and follow-up, at least 1 dose was adjusted, and at least 1 potentially hazardous drug was replaced by a safer alternative. We also assessed cumulative exposure to anticholinergic and sedative drugs as measured with the Drug Burden Index (DBI) (23) at follow-up.

Assessment of the primary and secondary pharmacologic outcomes was based on data from computerized pharmacy dispensing records. Data included the generic drug names, ATC codes, dosages, and start and stop dates for all prescribed medications between baseline and follow-up. All pharmacologic outcomes were reviewed and adjudicated by a panel consisting of the interns, an elder care physician who was not involved in conducting the 3MRs, and a professor of clinical pharmacy.

Secondary clinical outcome measures included the number of falls, visits to outpatient clinics, visits by elder care physicians, and consultations by other health care professionals (for example, physiotherapists), as documented in residents' medical charts. Cognitive function was assessed with the short form of the Severe Impairment Battery (SIB-S) (24) and the Mini-Mental State Examination (MMSE) (25) by trained assessors at baseline and follow-up. Nursing staff rated neuropsychiatric symptoms with the Neuropsychiatric Inventory–Nursing Home Version (NPI-NH) (26) (2 scores indicating "frequency × severity" and "staff workload/distress," both summed over 12 neuropsychiatric symptoms) and quality of life with the 3-level version of the EuroQol-5D instrument (EQ-5D-3L) (27) and the Dementia Quality-of-Life Instrument (DQI) (28). The following preplanned measures were not analyzed because of the small number of events: bone fractures (n = 7 [1.6%]), visits to emergency departments for gastrointestinal bleeding (n = 9 [2.1%]), and hospitalizations (n = 7 [1.6%]).

Statistical Analysis

In a power analysis, we expected that 40% of participants in the intervention group and 20% in the control group would successfully discontinue use of at least 1 inappropriate medication. Assuming 5% significance, 80% power, a cluster size of 15 residents, and an intracluster correlation coefficient of 0.1 (29), we estimated the required sample size to be 420 residents.

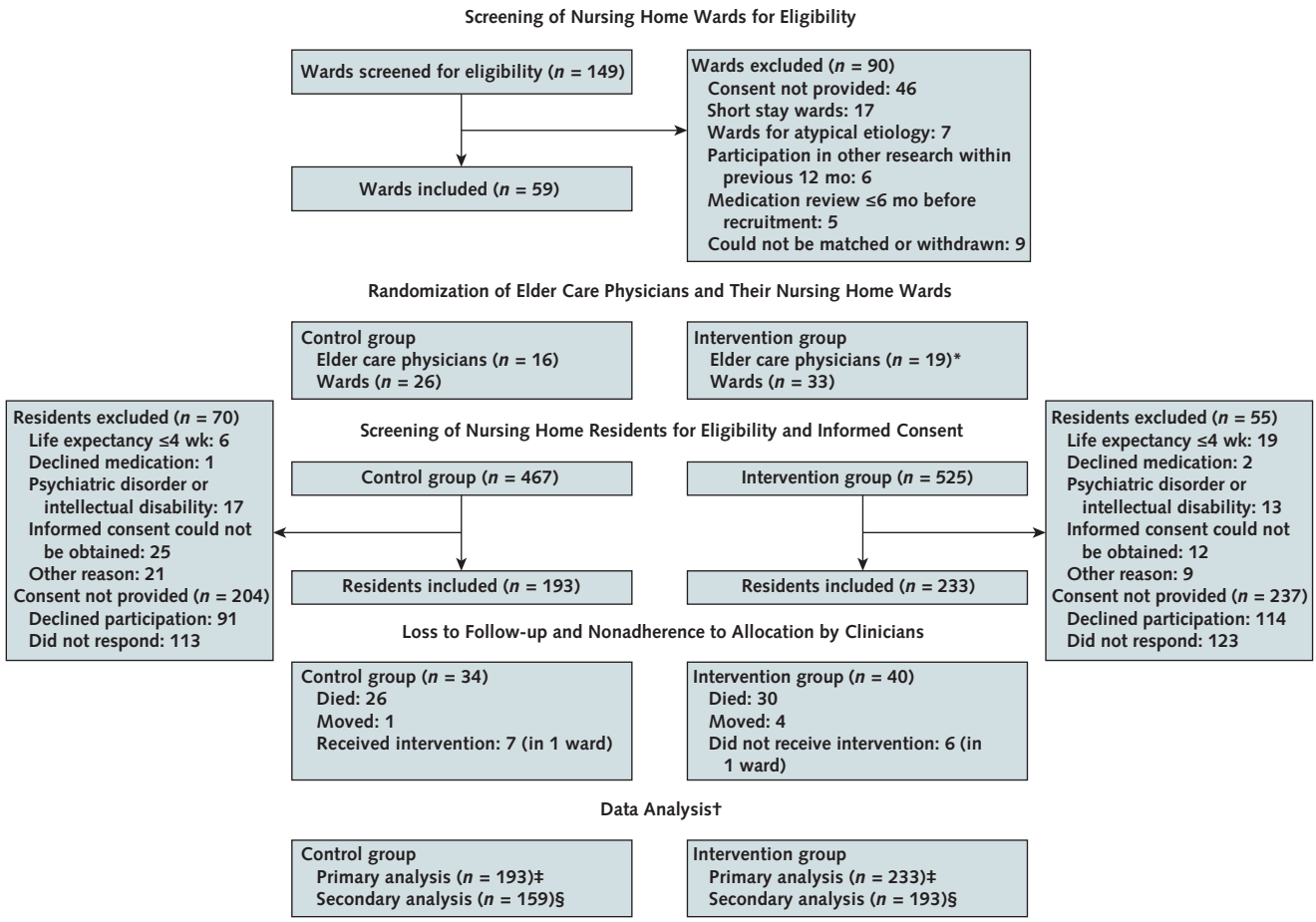
Clinical and demographic characteristics at the physician, ward, and resident levels were summarized with descriptive statistics. The effectiveness of the intervention (3MR) was examined with generalized linear mixed models. All models included a random intercept at the physician and ward levels to account for potential dependence of observations (that is, nursing home residents with the same physicians and wards). For binary outcomes at follow-up (successful discontinuation, initiation of underprescribed drugs, dose adjustments, and switches to safer alternatives [0 vs. ≥1 for each]), logistic mixed-model analyses were done and relative risks were estimated. In a post hoc analysis, the number of

Table 1. Overview of 3MR Steps

Step (Average Time Required per Resident)	Description
1. Assessing patient perspective and medical information (20 min)	Nursing home residents' experiences and preferences about their medicine use were assessed through a questionnaire completed by themselves or, if needed, with assistance by a member of the nursing staff or by their representatives. In preparation for step 2, pharmacy interns also compiled residents' diagnoses, allergies, and laboratory results from residents' medical charts and stored these in a database.
2. Drug reviewing (10 min)	Using the data collected in step 1 and the drugs prescribed to residents, the pharmacist reviewed the residents' medication in order to identify potential overprescribing and underprescribing and other suboptimal prescribing conditions. As part of this analysis, pharmacists used an automated prompt system with the START and STOPP criteria (21) and the Beers criteria (22).
3. Multidisciplinary meeting and pharmacotherapeutic actions (5 min)	In a meeting, the elder care physician and the pharmacist reviewed all information gathered in steps 1 and 2. If they could not determine the right indication for a medication (the correct diagnosis), the appropriate medical specialist was consulted. Actions to be taken on the basis of the findings from the review were agreed on by the elder care physician and the pharmacist (i.e., discontinuing and initiating drug use, dose adjustments, switches to safer alternatives, postponing decisions, arrangements to taper, and appointments about monitoring relapse symptoms and withdrawal effects).
4. Execution and evaluation of pharmacotherapeutic actions (10 min)	Actions to be taken on the basis of the findings from the multidisciplinary meeting were executed by the elder care physician and communicated with the nursing staff. These staff monitored adverse withdrawal and relapse events after discontinuation of medication use and other signs and symptoms due to other changes in drug prescribing. Elder care physicians also discussed medication changes with nursing home residents and/or their representatives.

3MR = Multidisciplinary Multistep Medication Review; START = Screening Tool to Alert Doctors to Right Treatment; STOPP = Screening Tool of Older Persons' Potentially Inappropriate Prescriptions.

Figure. Flow chart of inclusion and randomization of nursing home wards, elder care physicians, and nursing home residents.



* Includes 3 elder care physicians in 2 wards who contributed to the medication reviews in addition to the 16 physicians who were randomly assigned.
† Numbers for the primary outcome (successful discontinuation) are shown.
‡ Includes residents who were analyzed in the allocated group regardless of adherence by clinicians. Residents who were lost to follow-up were counted in the analyses as if medication use could not be successfully discontinued.
§ Includes only residents who were treated according to their allocation and were not lost to follow-up.

successfully discontinued drugs per resident was examined as a count variable in a Poisson mixed model.

For other count outcomes (falls [0, 1, or >1], outpatient clinic visits [0, 1, or >1], visits by elder care physicians [0 to 3, 4 to 6, 7 to 9, 10 to 14, or ≥15], and consultations by other health care professionals [0, 1 to 2, 3 to 4, 5 to 8, or ≥9]) and for both NPI-NH scores, we found overdispersion and therefore performed negative binomial mixed-model analyses and estimated rate ratios. For continuous outcomes (SIB-S, MMSE, DBI, EQ-5D-3L, and DQI scores at follow-up), the estimated differences between the groups were calculated from linear mixed models. In all analyses, we first estimated unadjusted effects. We then adjusted for residents' sex, age, marital status, length of nursing home stay, Charlson Comorbidity Index score, and dementia diagnosis by including these as fixed effects. Analyses of DBI score, cognitive function, neuropsychiatric symptoms, and quality of life were also adjusted for baseline values.

In the primary analysis, we included all residents regardless of clinicians' adherence to the allocated treatment. Residents who were lost to follow-up were counted as if medication use was not successfully discontinued. In a secondary analysis, we included only residents who were treated according to their allocation and were not lost to follow-up. In sensitivity analyses (**Appendix Table 1**, available at Annals.org), we examined the robustness of the findings for the primary outcome (successful discontinuation) by repeating the primary analysis for residents older than 65 years and those younger than 95 years, residents with at least 4 or fewer than 17 drugs prescribed at baseline, and residents with length of stay in the nursing home of at least 4 months or less than 87 months.

Because DBI score and the secondary clinical outcomes either required follow-up assessment (cognitive function, neuropsychiatric symptoms, and quality of life) or were meaningful only for residents who were present at follow-up (falls, outpatient clinic visits, visits

by elder care physicians, and consultations by other health care professionals), they were examined only in the secondary analysis that included only participants who completed follow-up. We estimated 95% CIs for all variables. All generalized linear mixed-model analyses were conducted with MLwiN, version 2.32 (Centre for Multilevel Modelling, University of Bristol), and all other analyses were done with SPSS Statistics for Windows, version 23.0 (IBM).

Role of the Funding Source

The Netherlands Organisation for Health Research and Development was not involved in the conception of the study design or the collection, analysis, interpretation, or publication of the data.

RESULTS

Of the 149 nursing home wards that were screened for eligibility, 59 were included. After randomization, 16 elder care physicians and 26 wards were allocated to the control group, and 16 elder care physicians and 33 wards were allocated to the intervention group. In addition, in 2 wards, medication reviews were delegated to 3 additional elder care physicians who also received brief preparatory training about the 3MR. Therefore, a total of 19 physicians were involved in the intervention. The 3MRs were done by the treating elder care physicians in collaboration with 5 pharmacists. A total of 992 nursing home residents (467 in the control group and 525 in the intervention group) were screened for eligibility, of whom 125 (70 in the control group and 55 in the intervention group) were excluded. Among those who were eligible, informed consent was obtained for 426 nursing home residents who were thus included (193 in the control group and 233 in the intervention group) (Figure). There were minor differences between the intervention and control groups in terms of the characteristics of physicians, wards, and residents (Table 2).

All medication reviews in the intervention group were done, but the physician could not implement the medication change in time for 6 of 233 (3%) residents (in 1 ward). Residents in the control group did not receive the intervention, except for 7 of 193 (4%) (in 1 ward) because of contractual obligations to perform a review. Overall, 2 of 233 residents in the intervention group and 2 of 193 in the control group used no medications at baseline.

Mean follow-up was 144 days (SD, 21) overall, 145 days (SD, 24) in the control group, and 142 days (SD, 19) in the intervention group. At follow-up, 56 nursing home residents had died (26 in the control group and 30 in the intervention group), and 5 had moved out of the nursing home ward (1 in the control group and 4 in the intervention group). Loss to follow-up was therefore 14.3% (14.0% in the control group and 14.6% in the intervention group).

Successfully discontinued drugs included drugs for the alimentary tract, cardiovascular drugs, drugs for disorders of the musculoskeletal system, drugs for the nervous system, and respiratory drugs (Appendix Table 2, available at Annals.org). Analysis of the primary outcome showed that use of at least 1 inappropriate medication was successfully discontinued in a greater proportion of nursing home residents from the intervention group (91 of 233 [39.1%]) than the control group (57 of 193 [29.5%]) (relative risk adjusted for covariates, 1.37 [95% CI, 1.02 to 1.75]) (Table 3). Analyses of the number of drugs successfully discontinued and the secondary analysis of data from participants with data available only at follow-up yielded similar results (Table 3).

The primary analysis (entire sample) and the secondary analysis (limited to participants who completed follow-up) showed no differences between the intervention and control groups for the other secondary pharmacologic outcomes (initiation of ≥1 underprescribed medication, dose adjustments, switches to safer drugs, and mean DBI score at follow-up) (Table 3). Similarly, the groups did not differ in the secondary clinical outcomes (falls, number of outpatient clinic visits, visits by elder care physicians, consultations by other health care professionals, cognitive function, neuropsychiatric symptoms, and quality of life) (Table 4).

DISCUSSION

Compared with usual care, 3MRs resulted in successful discontinuation of use of at least 1 drug in a greater proportion of nursing home residents. We observed a 10% improvement in the intervention group, which was smaller than the 20% anticipated in the power analysis; this could have been due to a lower

Table 2. Characteristics of Elder Care Physicians, Nursing Home Wards, and Nursing Home Residents

Characteristic	Control Group	Intervention Group
Elder care physicians, *n*	16	19
Working experience >5 y, *n (%)*	8 (50.0)	10 (52.6)
Female, *n (%)*	8 (50.0)	8 (42.1)
Physicians per number of wards, *n (%)*		
1 ward	8 (50)	10 (53)
2 wards	6 (37)	5 (26)
≥3 wards	2 (13)	4 (21)
Nursing home wards, *n*	26	33
Residents, *n*		
Mean (SD)	20 (10)	17 (10)
Median (IQR)	16 (9.8–30.0)	15 (9.0–23.5)
Wards for residents with dementia, *n (%)*	16 (62)	21 (64)
Urban location, *n (%)*	12 (46)	18 (55)
Nursing home residents, *n*	193	233
Mean age (SD), *y*	83.2 (8.9)	83.7 (9.5)
Female, *n (%)*	137 (71)	151 (65)
Married/partnered, *n (%)*	73 (38)	76 (33)
Mean length of stay (SD), *mo*	34.0 (26.3)	34.5 (31.9)
Mean Charlson Comorbidity Index score (SD)	2.0 (1.5)	2.0 (1.4)
Dementia, *n (%)*	87 (45)	99 (43)

IQR = interquartile range.

Table 3. Effects of 3MR on Successful Discontinuation of Medication Use and Secondary Pharmacologic Outcomes Among Nursing Home Residents in the Intervention and Control Groups

Variable	Control Group (*n* = 193)	Intervention Group (*n* = 233)	Treatment Difference (95% CI)	
			Unadjusted	Adjusted*
Primary analysis†				
Residents who successfully discontinued use of ≥1 inappropriate medication, *n (%)*	57 (29.5)	91 (39.1)	Relative risk: 1.35 (1.02 to 1.72)	Relative risk: 1.37 (1.02 to 1.75)
Residents who successfully discontinued inappropriate medication use, *n (%)*				
0 medications	136 (70.5)	142 (60.9)	–	–
1 medication	39 (20.2)	58 (24.9)	–	–
2 medications	8 (4.1)	16 (6.9)	–	–
≥3 medications	10 (5.2)	17 (7.3)	Rate ratio: 1.41 (0.96 to 2.06)	Rate ratio: 1.47 (1.01 to 2.16)
Residents who initiated use of ≥1 underprescribed medication, *n (%)*	14 (7.3)	39 (16.7)	Relative risk: 2.09 (0.82 to 4.63)	Relative risk: 2.09 (0.88 to 4.41)
Residents with ≥1 dose adjustment, *n (%)*	86 (44.6)	93 (39.9)	Relative risk: 0.88 (0.65 to 1.13)	Relative risk: 0.90 (0.67 to 1.16)
Residents with ≥1 switch to safer alternative, *n (%)*	2 (1.0)	5 (2.1)	Relative risk: 2.09 (0.40 to 10.04)	Relative risk: 2.46 (0.47 to 12.0)
	Control Group (*n* = 159)	**Intervention Group (*n* = 193)**		
Secondary analysis‡				
Residents who successfully discontinued use of ≥1 inappropriate medication, *n (%)*	55 (34.6)	85 (44.0)	Relative risk: 1.31 (0.98 to 1.65)	Relative risk: 1.33 (0.98 to 1.70)
Residents who successfully discontinued inappropriate medication use, *n (%)*				
0 medications	104 (65.4)	108 (56.0)	–	–
1 medication	38 (23.9)	55 (28.5)	–	–
2 medications	7 (4.4)	13 (6.7)	–	–
≥3 medications	10 (6.3)	17 (8.8)	Rate ratio: 1.40 (0.94 to 2.08)	Rate ratio: 1.42 (0.95 to 2.13)
Residents who initiated use of ≥1 underprescribed medication, *n (%)*	14 (8.8)	37 (19.2)	Relative risk: 1.97 (0.76 to 4.33)	Relative risk: 1.96 (0.80 to 4.14)
Residents with ≥1 dose adjustment, *n (%)*	81 (50.9)	88 (45.6)	Relative risk: 0.88 (0.65 to 1.13)	Relative risk: 0.90 (0.66 to 1.16)
Residents with ≥1 switch to safer alternative, *n (%)*	2 (1.3)	5 (2.6)	Relative risk: 2.09 (0.41 to 9.86)	Relative risk: 2.45 (0.46 to 11.67)
Mean DBI score at follow-up (SD)	1.43 (1.06)	1.60 (1.18)	Mean difference: −0.01 (−0.13 to 0.12)§	Mean difference: −0.02 (−0.15 to 0.11)§

3MR = Multidisciplinary Multistep Medication Review; DBI = Drug Burden Index.
* Adjusted for residents' sex, age, marital status, length of stay in nursing home, Charlson Comorbidity Index score, and dementia diagnosis.
† Residents' allocation was considered regardless of clinicians' adherence, and residents who were lost to follow-up were included in the analysis and counted as if medication use could not be successfully discontinued.
‡ Included only residents who were treated according to their allocation and were not lost to follow-up.
§ Also adjusted for baseline value.

response in the intervention group or improved prescribing in the control group. This finding is consistent with the findings of Patterson and colleagues (16) about discontinuation of inappropriate psychoactive drug use. Secondary pharmacologic outcomes (initiation of underprescribed drugs, dose adjustments, switches to safer drugs, and cumulative exposure to anticholinergic and sedative medication) were similar between the intervention and control groups at the end of follow-up. We found no differences in secondary clinical outcomes between the intervention and control groups in terms of cognitive function, neuropsychiatric symptoms, and quality of life. The number of falls, outpatient clinic visits, visits by elder care physicians, and consultations by other health care professionals also did not differ, although our study might have been underpowered to detect effects on these outcomes. Overall, our findings suggest that successful discontinuation of inappropriate medication use did not occur at the expense of further deterioration of nursing home residents' well-being.

Our findings have implications for research and clinical practice. First, we used several criteria to support the decision-making process during the medication reviews. Evidence-based deprescribing guidelines that are currently being developed (30) could be useful but were not available when we developed the 3MR. Second, the 3MR was done only once. This population often experiences a gradual and progressive functional decline and has a limited life expectancy. Longitudinal research may provide information about how often systematic medication reviews, such as the 3MR, should be done or how medication prescribing should be adjusted as treatment goals shift from curative or preventive treatment to palliative or comforting care. Third, nursing home residents' well-being is probably influenced by multiple factors. Multidomain interventions that combine medication reviews with better nutritional care, exercise, and psychosocial interventions might affect clinical outcomes. Finally, although we included the experiences and preferences of residents or their representatives in the 3MR (31), additional insight is needed on how to involve patients and representatives in the decision-making process around deprescribing, especially in the nursing home setting.

Our study has several limitations. When determining successful discontinuation, we could have missed withdrawal symptoms or relapses if they were mild or were not documented in residents' medical charts. In addition, we were unable to assess long-term disease relapse related to discontinuation of use of certain medications, such as preventive medication. However, we chose a follow-up period of 4 months to prevent excessive loss to follow-up because of the substantial mortality risk in this frail patient population. Although we used cluster randomization to prevent contamination bias, physicians from the intervention group collaborated closely with physicians from the control group in some nursing homes. However, such limitations are likely to increase the chance that actual effects are not detected (type II error), and despite their possible presence, we still observed favorable effects of the 3MR. Also, we cannot rule out that participants or assessors may have been aware of the allocation of wards. Finally, we enrolled nursing home residents from only the 3 northern provinces of the Netherlands.

This study also has several strengths, including its focus on nursing home residents, implementation of

Table 4. Effects of 3MR on Secondary Clinical Outcomes Among Nursing Home Residents in the Intervention and Control Groups*

Outcome†	Control Group (*n* = 159)	Intervention Group (*n* = 193)	Treatment Difference (95% CI)	
			Unadjusted	Adjusted‡
Harms and health care use				
Falls, *n (%)*				
0 falls	115 (72.3)	143 (74.1)	–	–
1 fall	28 (17.6)	27 (14.0)	–	–
>1 fall	16 (10.1)	23 (11.9)	Rate ratio: 0.94 (0.50 to 1.76)	Rate ratio: 0.98 (0.52 to 1.85)
Outpatient clinic visits, *n (%)*				
0 visits	144 (90.6)	163 (84.5)	–	–
1 visit	10 (6.3)	22 (11.4)	–	–
>1 visit	5 (3.1)	8 (4.1)	Rate ratio: 1.14 (0.44 to 2.96)	Rate ratio: 0.74 (0.27 to 2.00)
Elder care physician visits, *n (%)*				
0–3 visits	22 (13.8)	48 (24.9)	–	–
4–6 visits	33 (20.8)	37 (19.2)	–	–
7–9 visits	40 (25.2)	33 (17.1)	–	–
10–14 visits	36 (22.6)	30 (15.5)	–	–
≥15 visits	28 (17.6)	45 (23.3)	Rate ratio: 0.98 (0.77 to 1.24)	Rate ratio: 0.95 (0.75 to 1.20)
Consultations by other health care professionals, *n (%)*				
0 consultations	22 (13.8)	38 (19.7)	–	–
1–2 consultations	39 (24.5)	54 (28.0)	–	–
3–4 consultations	25 (15.7)	34 (17.6)	–	–
5–8 consultations	36 (22.6)	32 (16.6)	–	–
≥9 consultations	37 (23.3)	35 (18.1)	Rate ratio: 0.76 (0.49 to 1.17)	Rate ratio: 0.76 (0.50 to 1.15)
	Control Group (*n* = 157)	**Intervention Group (*n* = 184)**		
Cognitive function at follow-up				
Mean SIB-S score (SD)	27.3 (19.9)	30.1 (19.4)	Mean difference: 1.53 (−2.03 to 5.09)§	Mean difference: 1.03 (−2.47 to 4.54)§
Mean MMSE score (SD)	9.2 (9.0)	11.1 (10.1)	Mean difference: 0.29 (−1.29 to 1.86)§	Mean difference: 0.04 (−1.26 to 1.34)§
	Control Group (*n* = 146)	**Intervention Group (*n* = 170)**		
Neuropsychiatric symptoms at follow-up				
Mean NPI-NH score (SD): frequency × severity	22.2 (27.4)	14.0 (18.7)	Rate ratio: 0.80 (0.54 to 1.19)§	Rate ratio: 0.78 (0.53 to 1.15)§
Mean NPI-NH score (SD): staff workload/distress	9.5 (10.6)	6.8 (7.8)	Rate ratio: 0.96 (0.68 to 1.36)§	Rate ratio: 0.95 (0.67 to 1.35)§
Quality of life at follow-up				
Mean EQ-5D-3L utilities score (SD)	0.33 (0.26)	0.41 (0.27)	Mean difference: 0.05 (−0.01 to 0.11)§	Mean difference: 0.05 (−0.01 to 0.11)§
Mean DQI utilities score (SD)	0.34 (0.29)	0.46 (0.29)	Mean difference: 0.07 (0.01 to 0.14)§	Mean difference: 0.06 (−0.01 to 0.13)§

3MR = Multidisciplinary Multistep Medication Review; DQI = Dementia Quality-of-Life Instrument; EQ-5D-3L = 3-level version of the EuroQol-5D instrument; MMSE = Mini-Mental State Examination; NPI-NH = Neuropsychiatric Inventory-Nursing Home Version; SIB-S = short form of the Severe Impairment Battery.
* Percentages may not sum to 100 due to rounding.
† Examined only in the secondary analysis, which included only residents who were treated according to their allocation and were not lost to follow-up.
‡ Adjusted for residents' sex, age, marital status, length of stay in nursing home, Charlson Comorbidity Index score, and dementia diagnosis.
§ Also adjusted for baseline value.

the intervention in multiple nursing home wards, use of standardized medication reviews, and assessment of multiple pharmacologic outcomes. These pharmacologic outcomes were complemented by clinical outcomes relevant to patients, such as falls, cognitive function, and neuropsychiatric symptoms. Our primary outcome (successful discontinuation of inappropriate medication use) was a more appropriate outcome than the absolute number of discontinued drugs because it took into account potential withdrawal effects and relapses. Our cluster randomization was meant to prevent contamination associated with simple randomization of individual nursing home residents with the same elder care physician. Our methods also included a matching procedure to increase the likelihood of creating similar groups. The intervention and control groups were similar for potential demographic and clinical confounders.

Given the increasing prevalence of polypharmacy in older adults (32, 33), our study provides timely and practical guidance on how to operationalize deprescribing in nursing home residents (9, 30, 31). Our findings demonstrate the positive effects of the 3MR on decreasing inappropriate prescribing without compromising the well-being of vulnerable nursing home residents.

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Acknowledgment: The authors thank the nursing home residents, their family members, and the health professionals involved in the study for their contributions. They also thank Dr. Roel Grol and Dr. Simon Horsburgh for commenting on earlier versions of the manuscript.

Grant Support: By the Netherlands Organisation for Health Research and Development (grant 80-83600-98-10176).

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-2729.

Reproducible Research Statement: *Study protocol:* See the Supplement and reference 20. *Statistical code and data set:* Available from Prof. Taxis (e-mail, k.taxis@rug.nl).

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Appendix Table 1. Sensitivity Analyses of Effects of 3MR on Primary Outcome (Successful Discontinuation)*

Variable	Control Group	Intervention Group	Relative Risk (95% CI)†
Age, *n/N (%)*			
>65 y	56/187 (30)	87/220 (40)	1.34 (1.01–1.71)
<95 y	53/182 (29)	87/218 (40)	1.37 (1.04–1.73)
Drugs prescribed at baseline, *n/N (%)*			
≥4 drugs	55/183 (30)	91/217 (42)	1.40 (1.07–1.75)
<17 drugs	54/180 (30)	81/212 (38)	1.27 (0.96–1.62)
Length of stay in nursing home, *n/N (%)*			
≥4 mo	53/178 (30)	87/219 (40)	1.35 (1.02–1.71)
<87 mo	53/175 (30)	87/217 (40)	1.36 (1.01–1.74)

3MR = Multidisciplinary Multistep Medication Review.
* Analyses according to primary analysis.
† Unadjusted estimates.

Appendix Table 2. Types of Successfully Discontinued Drugs

ATC* Drug Classes and Corresponding Medications	Successfully Discontinued Drugs, *n*	
	Control Group	Intervention Group
A0: Stomatological preparations, drugs for acid-related disorders, drugs for functional gastrointestinal disorders, drugs for constipation	15	19
A1: Drugs used in diabetes, vitamins, mineral supplements	8	14
B0: Antithrombotic agents, antianemic preparations	9	24
C0: Cardiac therapy, antihypertensives, diuretics, β-blockers, calcium-channel blockers, agents acting on the renin–angiotensin system	16	19
C1: Lipid-modifying agents	0	6
G0: Sex hormones and modulators of the genital system, urological drugs	3	5
H0: Corticosteroids for systemic use	0	1
J0: Antibacterials for systemic use	0	2
L0: Immunosuppressants	0	1
M0: Anti-inflammatory and antirheumatic products, muscle relaxants, drugs for treatment of bone disease, other drugs for disorders of the musculoskeletal system	7	10
N0: Anesthetics, analgesics, antiepileptics, anti-Parkinson drugs, psycholeptics, psychoanaleptics	24	48
R0: Drugs for obstructive airway disease, cough and cold preparations, antihistamines for systemic use	4	8
S0: Ophthalmologic drugs	2	3
Other therapeutic drugs	5	2
Total	93	162

ATC = Anatomical Therapeutic Chemical.
* See www.whocc.no/atc_ddd_index for more information.