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Physician Antipsychotic Overprescribing Letters and Cognitive, Behavioral, and Physical Health Outcomes Among People With Dementia

A Secondary Analysis of a Randomized Clinical Trial

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Abstract

IMPORTANCE Antipsychotics, such as quetiapine, are frequently prescribed to people with dementia to address behavioral symptoms but can also cause harm in this population.

OBJECTIVE To determine whether warning letters to high prescribers of quetiapine can successfully reduce its use among patients with dementia and to investigate the impacts on patients' health outcomes.

DESIGN, SETTING, AND PARTICIPANTS This is a secondary analysis of a randomized clinical trial of overprescribing letters that began in April 2015 and included the highest-volume primary care physician (PCP) prescribers of quetiapine in original Medicare. Outcomes of patients with dementia were analyzed in repeated 90-day cross-sections through December 2018. Analyses were conducted from September 2021 to February 2024.

INTERVENTIONS PCPs were randomized to a placebo letter or 3 overprescribing warning letters stating that their prescribing of quetiapine was high and under review by Medicare.

MAIN OUTCOMES AND MEASURES The primary outcome of this analysis was patients' total quetiapine use in days per 90-day period (the original trial primary outcome was total quetiapine prescribing by study PCPs). Prespecified secondary outcomes included measures of cognitive function and behavioral symptoms from nursing home assessments, indicators of depression from screening questionnaires in assessments and diagnoses in claims, metabolic diagnoses derived from assessments and claims, indicators of use of the hospital and other health care services, and death. Outcomes were analyzed separately for patients living in nursing homes and in the community.

RESULTS Of the 5055 study PCPs, 2528 were randomized to the placebo letter, and 2527 were randomized to the 3 warning letters. A total of 84 881 patients with dementia living in nursing homes and 261 288 community-dwelling patients with dementia were attributed to these PCPs. There were 92 874 baseline patients (mean [SD] age, 81.5 [10.5] years; 64 242 female [69.2%]). The intervention reduced quetiapine use among both nursing home patients (adjusted difference, −0.7 days; 95% CI, −1.3 to −0.1 days; $P = .02$) and community-dwelling patients (adjusted difference, −1.5 days; 95% CI, −1.8 to −1.1 days; $P < .001$). There were no detected adverse effects on cognitive function (cognitive function scale adjusted difference, 0.01; 95% CI, −0.01 to 0.03; $P = .19$), behavioral symptoms (agitated or reactive behavior adjusted difference, −0.2%; 95% CI −1.2% to 0.8% percentage points; $P = .72$), depression, metabolic diagnoses, or more severe outcomes, including hospitalization and death.

(continued)

Key Points

Question Did overprescribing warning letters to high-volume primary care physician prescribers of the antipsychotic quetiapine reduce quetiapine use by their patients with dementia without harming patient health outcomes?

Findings In this secondary analysis of a randomized clinical trial, overprescribing warning letters significantly reduced quetiapine use among patients with dementia living in nursing homes and in the community. There were no detected adverse effects on indicators of cognitive, behavioral, and physical health.

Meaning This study found that warning letters informed by behavioral science can safely reduce overprescribing to patients with dementia, and related interventions may be broadly useful in promoting guideline-concordant care.

+ Visual Abstract

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE This study found that overprescribing warning letters to PCPs safely reduced quetiapine prescribing to their patients with dementia. This intervention and others like it may be useful for future efforts to promote guideline-concordant care.

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Introduction

Off-label use of antipsychotics in patients with dementia is commonplace. Approximately 1 in 7 nursing home residents receives an antipsychotic every quarter, and a similar share of people with dementia who live in the community receive an antipsychotic annually.[1-3] Rates of antipsychotic use in older adults with dementia have declined but prescribing persists at high levels.[4] Antipsychotics are frequently prescribed off-label to treat behavioral symptoms of dementia such as agitation and aggression. Although there is some evidence supporting this use, it can also cause substantial harm.[5,6] Studies have linked antipsychotic use among people with dementia to increased risks of weight gain, cognitive decline, falls and other injuries, cerebrovascular events, and mortality.[7-10]

Specialty societies and regulators have, therefore, promoted more judicious use of antipsychotics in dementia care.[11-15] However, studies on reducing prescribing largely consist of small trials or observational analyses, and evidence from large-scale randomized studies remains limited.[16-19] In practice, efforts to further reduce antipsychotic prescribing might achieve modest benefit or could even harm patients. For instance, ongoing antipsychotic use may occur in settings that lack the staffing and other resources to provide effective alternative interventions to ensure patient safety.[20,21]

We seek to fill this gap in empirical evidence through a secondary analysis of a large randomized letter trial that focused on the antipsychotic quetiapine. Quetiapine is the most-prescribed antipsychotic in the US and is frequently used among patients with dementia.[22,23] The trial enrolled approximately the top 5% of primary care physician (PCP) prescribers of quetiapine in Medicare. A random half of these PCPs were sent a series of overprescribing warning letters about their prescribing of quetiapine. The primary evaluation of this trial found that the letters substantially reduced quetiapine prescribing for at least 2 years.[24] However, that evaluation studied a considerably smaller patient sample and did not examine health outcomes beyond hospital visits. The current analysis uses linkages to claims and nursing home assessments to evaluate the effects of the letters on health outcomes among these PCPs' patients with dementia.

In this analysis, we followed patients with dementia over multiple years and evaluated effects on several behavioral, cognitive, metabolic, and other physical health outcomes. These end points align with the adverse effects of quetiapine and other antipsychotics like weight gain that might improve with deprescribing, as well as the potential benefits of these medications like reduced agitation that could deteriorate with indiscriminate deprescribing.

Methods

Trial Design

The design of the randomized clinical trial has been described elsewhere,[24] and we review it briefly here (the trial protocol is also shown in Supplement 1). The Centers for Medicare & Medicaid Services identified the highest-volume PCP prescribers of quetiapine in Medicare. They were allocated (1:1 ratio) to treatment and control groups using a random sequence of numbers. The Centers for Medicare & Medicaid Services sent treatment group PCPs a series of 3 overprescribing warning letters stating that their quetiapine prescribing was high relative to their peers and was under review by Medicare. The protocol

for the current secondary analysis (Supplement 1) provides a reproduction of a sample letter. Control PCPs were sent a placebo letter and clarification letter about an unrelated regulation. Initial letter mailings to both groups occurred in April 2015. Follow-up treatment letters were sent in August and October 2015. The original evaluation followed the PCPs and a cohort of patients for 2 years, until April 2017.

This secondary evaluation analyzes patients' outcomes through December 2018. It was approved by the institutional review boards of Columbia University (New York, New York) and the National Bureau of Economic Research (Cambridge, Massachusetts) as research exempt from informed consent requirements because the data were deidentified, in accordance with 45 CFR §46. The investigators prespecified the analysis plan for the nursing home sample with data blinded to the treatment status of PCPs and publicly archived it in January 2022 before unblinding. They followed the same process for the community-dwelling sample and archived the plan in August 2022.[25] The current analyses were conducted from September 2021 to February 2024. This study follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Data Sources

We used 2014 to 2018 Medicare fee-for-service claims, Part D prescribing, Minimum Data Set nursing home assessment, and Medicare enrollment data. The data contain records for 100% of study PCPs' fee-for-service Medicare patients with dementia during this period.

Study Sample

Our analytic samples consist of patients with dementia receiving care from the study PCPs between 2014 and 2018 residing in nursing homes (nursing home sample) and in the community (community-dwelling sample). In each sample, we assembled repeated cross-sections of patients during 90-day periods relative to study initiation on April 20, 2015, making the unit of analysis the patient-quarter. For instance, outcomes for the first postintervention cohort were measured from April 20 to July 18, 2015.

To define the set of patients in each cohort, we conducted standard prospective claims-based attribution[26,27] and matched patients to the clinician (physician or advanced practice practitioner) from whom they received the most outpatient or nursing home–based evaluation and management charges in the 90-day (for nursing home patients) or 180-day (for community-dwelling patients) time window directly preceding each period. For the nursing home sample, we only counted evaluation and management services in nursing facilities and used a 90-day window because we expected more frequent practitioner encounters in this sample. We then selected the patients attributed to study PCPs.

We restricted each cohort to patients in fee-for-service Medicare Parts A and B with Part D coverage during the outcome period and time window used for attribution. To limit to patients with dementia, we required a dementia diagnosis during or before the attribution window in the Medicare Chronic Conditions file. Each cohort, therefore, consists of patients with 1 or more dementia diagnosis codes in claims from approximately the previous 3 years.

Nursing home patients were those residing in a nursing home or skilled nursing facility on the last day of the window used for attribution. We excluded patients having a Medicare-covered skilled nursing stay on this day because prescribing during these stays is not covered by Part D. Patients who received no nursing home assessments during the outcome period were also excluded because we could not measure their nursing home–specific outcomes. Community patients were those who did not reside in a nursing facility on the last day of the attribution window. By construction, the same patient could only enter both samples in different quarters.

Patient Outcomes

The primary end point was the days of quetiapine received in the 90-day outcome period, as measured by the patient's prescription drug fills. This end point captures quetiapine treatment initiations and changes in receipt among continuing patients. We also analyzed a variety of claims-based secondary outcomes to measure changes in patients' health and health care use. These outcomes include depression and metabolic diagnoses, health care encounters, and death. Diagnosis

outcomes were defined as the patient having at least 1 inpatient, outpatient, skilled nursing, or professional claim with a relevant diagnosis code.

For patients in nursing homes, we constructed additional health indicators from the assessment data, such as measures of patients' cognitive function (Cognitive Function Scale),[28] behavioral symptoms (Agitated and Reactive Behavior Scale),[29] and depression screening (PHQ-9; Patient Health Questionnaire–9).[30] These scales have been extensively validated and provide a single overall measurement of each outcome domain. We defined a positive depression screen as a PHQ-9 score of 10 or higher.[31,32]

We further analyzed alternative measures of quetiapine use, such as prescriptions by the patient's attributed PCP, any prescriptions, and milligrams prescribed. We also studied potential patterns of substitution toward other antipsychotics, including first-generation and second-generation agents, and other psychoactive medication classes frequently used in dementia management, specifically antidepressants, benzodiazepines, gabapentinoids, mood stabilizers, and other sedative-hypnotics.

Statistical Analysis

To estimate the effect of letters on the primary and secondary end points, we used multivariable regression. The study took a modified intention-to-treat approach by analyzing patients of study PCPs according to methods described in the Study Sample subsection. We adjusted for period, patient-level and prescriber-level end points as measured at baseline, and patient-level demographic characteristics to increase the precision of estimates.[33] All models used robust variance techniques by clustering SEs at the level of the attributed PCP (the level of randomization).[34] Two-sided hypothesis tests with $P < .05$ were considered significant. Secondary end points were treated as exploratory and were not adjusted for multiple comparisons.

We conducted exploratory subgroup analyses by patient race and ethnicity, age, sex, and Medicare-Medicaid dual eligibility status. Race and ethnicity were extracted from Medicare enrollment data to assess potential inequities in the effects of the letters. We also divided the nursing home sample according to 3 facility indicators: the share of long-stay residents receiving an antipsychotic, the star rating for safety inspection deficiencies, and the star rating for staffing. Data were analyzed using Stata/MP statistical software version 17.0 (StataCorp).

Results

Of the 5055 prescribers in the original trial, 2528 were randomized to the placebo letter, and 2527 were randomized to the 3 warning letters. Among those in the trial, 1885 prescribers had nursing home patients, and 4584 had community-dwelling patients, with some having patients in both settings (eFigure 1 in Supplement 2). A total of 84 881 patients living in nursing homes and 261 288 community-dwelling patients were attributed to study prescribers. There were 92 874 baseline patients (mean [SD] age, 81.5 [10.5] years; 64 242 female [69.2%]). Among 22 333 baseline nursing home patients, the mean (SD) age was 82.9 (10.5) years, 16 233 (72.7%) were female, 3526 (15.8%) were Black, 1289 (5.8%) were Hispanic, 16 898 (75.7%) were White, and 620 (2.8%) were of other races (American Indian/Alaska Native, Asian/Pacific Islander, other, and unknown). Among the 70 541 baseline community-dwelling patients, the mean [SD] age was 81.1 (10.5) years, 48 009 (68.1%) were female, 7409 (10.5%) were Black, 9669 (13.7%) were Hispanic, 49 495 (70.2%) were White, and 3968 (5.6%) were of other races. Baseline patients in both groups were frequently prescribed quetiapine: those in nursing homes received a mean (SD) of 12.3 (36.7) days of quetiapine per quarter whereas those in the community received 10.3 (31.3) days (**Table 1** and **Table 2**). In the nursing home sample, study PCPs had a mean (SD) of 11.7 (18.6) dementia patients in nursing homes and prescribed quetiapine to 1.5 of them at baseline. PCPs in the community sample had a mean (SD) of 15.4 (19.6) community-dwelling patients at baseline and prescribed quetiapine to 1.8 patients.

Prescribing Outcomes

Across all postintervention periods, the mean (SD) days of quetiapine received by nursing home patients was 10.3 (34.2) in the control group and 10.1 (33.6) in the treatment group. Letters reduced quetiapine receipt by 0.7 days (adjusted difference; 95% CI, −1.3 to −0.1 days; $P = .02$), or 6.7% of the control mean (**Table 3**). Among community-dwelling patients, the mean (SD) days of quetiapine receipt was 9.9 (31.4) in the control group and 8.2 (28.6) in the treatment group. In this sample, letters reduced quetiapine receipt by 1.5 days (adjusted difference; 95% CI, −1.8 to −1.1 days; $P < .001$), or 14.8% of the control mean.

Among nursing home patients, reductions in quetiapine receipt were concentrated in the first 6 quarters of the study, whereas reductions persisted for the entire 15 quarter postintervention period among patients in the community (**Figure 1**). Restricting the analysis of nursing home patients to the first

Table 1. Baseline Characteristics of Study Patients With Dementia

Characteristic	Patients, No. (%) (N = 92 874)			
	Nursing home sample		Community-dwelling sample	
	Control (n = 11 925)	Treatment (n = 10 408)	Control (n = 36 605)	Treatment (n = 33 936)
Quetiapine receipt, mean (SD)				
Days	12.0 (36.5)	12.7 (36.9)	10.4 (31.5)	10.2 (31.1)
Days from attributed primary care physician	10.3 (33.9)	10.8 (34.1)	7.2 (26.0)	7.0 (25.6)
Any receipt	1478 (12.4)	1367 (13.1)	4392 (12.0)	4027 (11.9)
Milligrams, mean (SD)	1225 (5809)	1356 (6061)	1106 (5390)	1161 (5672)
Age, mean (SD), y	82.8 (10.5)	82.9 (10.5)	81.3 (10.5)	80.9 (10.5)
Sex				
Female	8656 (72.6)	7577 (72.8)	25 070 (68.5)	22 939 (67.6)
Male	3269 (27.4)	2831 (27.2)	11 535 (31.5)	10 997 (32.4)
Race and ethnicity				
Black	1897 (15.9)	1629 (15.7)	3812 (10.4)	3597 (10.6)
Hispanic	715 (6.0)	574 (5.5)	4662 (12.7)	5007 (14.8)
White	8997 (75.4)	7901 (75.9)	25 999 (71.0)	23 496 (69.2)
Other[a]	316 (2.6)	304 (2.9)	2132 (5.8)	1836 (5.4)
Chronic conditions, mean (SD), No.	5.0 (2.3)	5.0 (2.3)	5.0 (2.5)	5.0 (2.5)
Time since first dementia diagnosis, mean (SD), y	5.4 (3.9)	5.4 (3.9)	4.0 (3.6)	3.9 (3.5)
Days in nursing home	705.7 (841.3)	701.2 (816.4)	Not applicable	Not applicable
Dual Medicare-Medicaid eligible	8089 (67.8)	7081 (68.0)	15 217 (41.6)	14 841 (43.7)

[a] Includes patients with a race code of American Indian/Alaska Native, Asian/Pacific Islander, other, and unknown.

Table 2. Characteristics of Study PCPs

Characteristic	PCPs, No. (%) (N = 5055)[a]			
	Nursing home sample		Community-dwelling sample	
	Control (n = 958)	Treatment (n = 927)	Control (n = 2303)	Treatment (n = 2281)
Primary specialization[b]				
General practitioner	23 (2.4)	23 (2.5)	84 (3.6)	99 (4.3)
Family medicine	435 (45.4)	427 (46.1)	1058 (45.9)	1098 (48.1)
Internal medicine	500 (52.2)	477 (51.5)	1161 (50.4)	1084 (47.5)
Any specialization code for geriatrics	80 (8.4)	96 (10.4)	147 (6.4)	154 (6.8)
Sex				
Female	128 (13.4)	122 (13.2)	389 (16.9)	393 (17.2)
Male	830 (86.6)	805 (86.8)	1914 (83.1)	1888 (82.8)
Patients with dementia at baseline, mean (SD), No.[c]				
Total	12.3 (19.2)	11.1 (18.0)	15.9 (21.4)	14.9 (17.7)
Prescribed quetiapine	1.5 (2.7)	1.5 (2.8)	1.9 (3.5)	1.8 (3.3)
Prescribed any antipsychotics	3.3 (5.7)	3.0 (5.4)	3.4 (5.7)	3.1 (5.4)

Abbreviation: PCP, primary care physician.

[a] Among these PCPs, 1853 treated patients living in both settings and 32 did not treat any patients in either setting.

[b] A small number of practitioners (<11) in the community-dwelling sample later changed their specialization to a field outside primary care. We classify them here by the primary care specialization that triggered their entry into the study.

[c] Number of patients at baseline attributed to study PCP. Refers to nursing home patients or community-dwelling patients as given by the column heading.

6 quarters, letters reduced quetiapine use by 1.1 days per quarter (adjusted difference; 95% CI, −1.6 to −0.5 days; $P < .001$; control mean, 11.2 days; treatment mean, 10.5 days) (eTable 1 in Supplement 2).

Relative effects were similar using other measures of quetiapine use. In both samples, there was no detected effect on use of other antipsychotics. There were no significant changes in receipt of other psychoactive medications commonly used in dementia management, including those used off-label to manage behavioral symptoms like antidepressants[35] and mood stabilizers[23] (eTable 2 in Supplement 2).

Health Outcomes

Nursing Home Patients

Among nursing home patients, there were no statistically significant adverse changes in cognitive or behavioral health measures coincident with the decline in quetiapine use. Specifically, there was no detected effect on cognitive function (mean [SD] score, 2.6 [0.99] for control vs 2.6 [0.98] for treatment; adjusted difference, 0.01; 95% CI, −0.01 to 0.03; $P = .19$; scale range 1-4 with higher values indicating more limited function). We also found no detectable effect on the share of patients

Table 3. Effect of the Intervention on Primary and Secondary Outcomes[a]

Variable	Nursing home patients			Community-dwelling patients		
	Control group, No. (%)[b]	Adjusted difference, d (95% CI)	*P* value	Control group, No. (%)[b]	Adjusted difference, d (95% CI)	*P* value
Prescribing						
Quetiapine receipt						
Days, mean (SD)	10.3 (34.2)	−0.7 (−1.3 to −0.1)	.02	9.9 (31.4)	−1.5 (−1.8 to −1.1)	<.001
Days from attributed primary care physician, mean (SD)	8.6 (31.1)	−0.7 (−1.3 to −0.2)	.01	6.6 (25.2)	−1.3 (−1.5 to −1.0)	<.001
Any receipt	16 647 (10.4)	−0.6 (−1.2 to −0.1)	.03	54 871 (11.0)	−1.6 (−1.9 to −1.3)	<.001
Milligrams, mean (SD)	1057 (5362)	−64 (−139 to 12)	.10	1024 (5112)	−121 (−161 to −81)	<.001
Receipt of other antipsychotics						
Days, mean (SD)	13.0 (37.0)	0.4 (−0.2 to 0.9)	.24	8.2 (29.3)	0.1 (−0.2 to 0.3)	.58
Any receipt	22 404 (14.0)	0.4 (−0.2 to 1.0)	.17	45 800 (9.2)	0.2 (−0.1 to 0.5)	.15
Received other psychiatric medication	103 646 (64.9)	−0.2 (−1.1 to 0.6)	.59	269 974 (54.1)	0.0 (−0.4 to 0.5)	.91
Cognitive and behavioral health						
Cognitive function scale score, mean (SD)[c]	2.58 (0.99)	0.01 (−0.01 to 0.03)	.19	NA	NA	NA
Agitated or reactive behavior	29 570 (18.6)	−0.2 (−1.2 to 0.8)	.72	NA	NA	NA
Depression screen positive[d]	8340 (5.3)	−0.5 (−1.2 to 0.2)	.13	NA	NA	NA
Depression diagnosis	48 859 (30.6)	−1.3 (−2.6 to 0.1)	.07	85 955 (17.2)	−0.5 (−1.1 to 0.1)	.07
Metabolic indicators and diagnoses						
Weight loss	12 422 (7.8)	0.3 (−0.0 to 0.7)	.06	NA	NA	NA
Body mass index, mean (SD)[e]	26.4 (6.5)	−0.0 (−0.1 to 0.1)	.57	NA	NA	NA
Diabetes diagnosis	55 499 (34.8)	−0.1 (−0.9 to 0.6)	.70	158 309 (31.7)	0.1 (−0.4 to 0.6)	.70
Hyperlipidemia diagnosis	45 481 (28.5)	−0.1 (−1.5 to 1.4)	.94	193 232 (38.7)	0.6 (−0.2 to 1.4)	.15
Hypertension diagnosis	111 049 (69.5)	−0.0 (−1.5 to 1.4)	.95	316 600 (63.5)	−0.1 (−0.7 to 0.6)	.83
Hyperglycemia diagnosis	2693 (1.7)	−0.1 (−0.3 to 0.1)	.53	18 522 (3.7)	0.2 (−0.2 to 0.7)	.32
Other indicators of adverse events						
Death	6833 (4.3)	0.0 (−0.1 to 0.2)	.65	20 834 (4.2)	−0.1 (−0.3 to −0.0)	.04
Any emergency department visit	17 087 (10.7)	0.3 (−0.3 to 0.8)	.31	79 238 (15.9)	0.1 (−0.2 to 0.4)	.54
Any inpatient stay	17 889 (11.2)	−0.3 (−0.7 to 0.1)	.19	66 331 (13.3)	0.0 (−0.3 to 0.3)	.81
Entry to skilled nursing facility or nursing facility	NA	NA	NA	22 607 (4.5)	−0.0 (−0.2 to 0.1)	.68
Any use of restraints	2660 (1.7)	−0.0 (−0.3 to 0.3)	.92	NA	NA	NA

Abbreviation: NA, not applicable.

[a] All outcomes were measured within 90-day periods and were based on claims and assessments with dates of service or target dates during the period. The number of observations is 299 729 patient-periods (84 881 distinct patients) for the nursing home sample and 965 510 patient-periods (261 288 distinct patients) for the community-dwelling sample. For the nursing home sample, assessment outcomes are occasionally missing and effective sample sizes may be slightly smaller (minimum number of observations 290 861).

[b] Control group number of observations in patient-periods is provided for binary outcomes.

[c] Measured by the Cognitive Function Scale, ranging from 1 (cognitively intact) to 4 (severely impaired).

[d] Defined as a Patient Health Questionnaire-9 score of 10 or higher.

[e] Body mass index is calculated as weight in kilograms divided by height in meters squared.

with any agitated or reactive behavior (control mean, 18.6%; treatment mean, 18.5%; adjusted difference −0.2%; 95% CI, −1.2% to 0.8%; *P* = .72).

Measures of depression rates were similar but generally lower in the treatment group compared with control. Specifically, the share with screen positive depression was not significantly different (control mean, 5.3%; treatment mean, 4.3%; adjusted difference, −0.5%; 95% CI, −1.2% to 0.2%; *P* = .13) nor was share with depression diagnoses in claims (control mean, 30.6%; treatment mean, 28.4%; adjusted difference, −1.3%; 95% CI, −2.6% to 0.1%; *P* = .07). Alternative constructions of cognitive, behavioral, and mental health end points yielded similar results (eTable 3 in Supplement 2).

A higher percentage of treatment patients reported weight loss vs the control group, although the difference was not significant (control mean, 7.8%; treatment mean, 8.1%; adjusted difference, 0.3%; 95% CI, −0.0% to 0.7%; *P* = .06). Rates of metabolic diagnoses in claims were similar in the treatment and control groups. Indicators of more severe adverse outcomes, including emergency department use, inpatient hospital admission, death, and use of restraints, were not significantly different between treatment and control groups. Analyses of further prespecified outcomes also did not suggest harm (eTable 4 in Supplement 2).

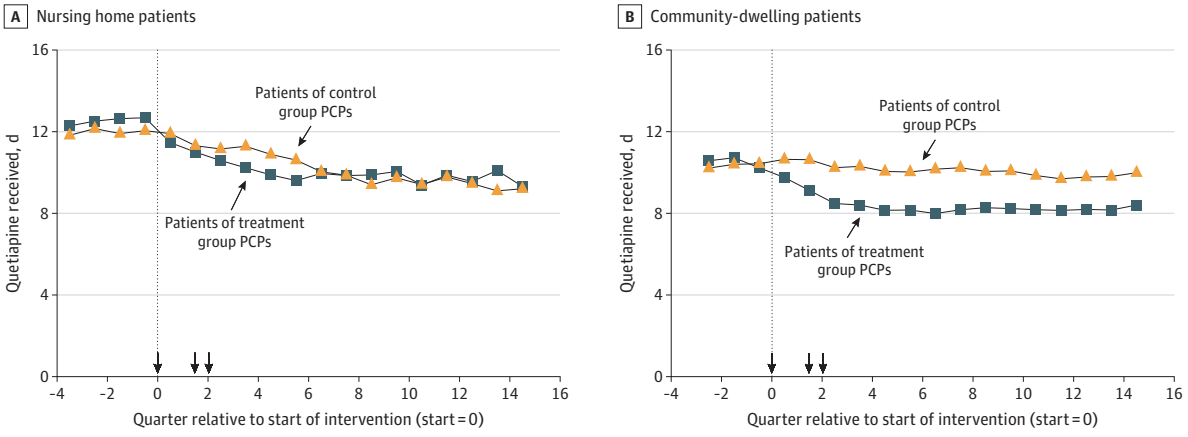
Community-Dwelling Patients

Results were similar for patients living in the community, although only claims-based health indicators were available for this population. As we observed for patients living in nursing homes, there was a decrease in the share with depression diagnoses that was not statistically significant (control mean, 17.2%; treatment mean, 16.6%; adjusted difference, −0.5%; 95% CI, −1.1% to 0.1%; *P* = .07). There were no detected adverse impacts on more severe health end points, including rates of hospital use or entry to nursing facilities. The risk of death was statistically significantly lower for treated vs control patients (control mean, 4.2%; treatment mean, 3.9%; adjusted difference, −0.1%; 95% CI, −0.3% to −0.0%; *P* = .04).

Subgroup Analyses

Among nursing home patients, reductions in quetiapine receipt were particularly pronounced among relatively young (aged 65-74 years) and relatively old (aged ≥95 years) individuals (**Figure 2**A). Although deprescribing was statistically significant for White patients only, the effects were measured imprecisely for other groups owing to smaller subgroup samples. In turn, we fail to reject that the reduction in quetiapine receipt was the same across racial and ethnic groups. Impacts

Figure 1. Time Series of Quetiapine Receipt for Treatment and Control Patients



Each point represents the mean days of quetiapine received by patients of treatment and control group study primary care physicians (PCPs) during 90-day periods relative to study initiation in April 2015. The number of observations within each group and quarter ranges between 8658 and 13 114 patients for the nursing home sample (A) and between 29 347 and 39 506 patients for the community sample (B). Patients with multiple study PCPs across periods are included in the time series. Arrowheads on x-axis denote when warning letters were sent to treatment group PCPs.

appeared to focus on individuals who were not dually eligible for Medicare and Medicaid, although differences were not clearly distinguishable. The effects were large and statistically significant in nursing homes with poorer star ratings and lower prestudy levels of antipsychotic prescribing.

Among patients living in the community, reductions in quetiapine prescribing were comparatively similar across subgroups (Figure 2B). In this sample, differences on the basis of race, ethnicity, and dual eligibility status were muted compared with the nursing home sample.

There were no consistent signs of harm across key nursing home assessment–based health outcomes (eFigure 2 in Supplement 2) and key claims-based health outcomes (eFigures 3 and 4 in Supplement 2) in the subgroups. In turn, subgroups that experienced more substantial deprescribing, like White and/or non–dually eligible nursing home patients, did not show corresponding deteriorations in these indicators.

Discussion

This secondary analysis of a randomized clinical trial provides evidence that a low-cost letter intervention informed by behavioral science can reduce prescribing of quetiapine to patients with dementia in nursing home and community settings. Lower levels of quetiapine use were not accompanied by adverse health outcomes, including adverse changes in cognitive function, behavioral symptoms, metabolic diagnoses, and hospitalization. We further found encouraging, although not statistically significant, differences in rates of depression diagnoses in the direction of benefit. There were also signs of decreased risk of death among patients living in the community. Taken together, these findings suggest that the deprescribing induced by the letters was unlikely to harm and may have helped patients.

This evaluation provides new evidence on the value of ongoing interventions to reduce antipsychotic use in dementia care. It addresses several limitations of previous trials[16,17,19] that had suggested deprescribing could be done safely. The sample size of the present study was 2 to 3 orders of magnitude greater than that of previous trials, greatly increasing statistical power to detect patient harms. Nevertheless, our large-scale study reaffirms the potential for interventions to promote safe deprescribing. This intervention was also conducted when second-generation antipsychotics were dominant, further increasing its relevance for contemporary practice. Finally, the letter approach evaluated here is likely lower-cost than many alternative interventions.

Reductions in quetiapine use were larger and more durable among patients with dementia who lived in the community, pointing to the potential for interventions to promote long-lasting deprescribing. These impacts may reflect the stronger language of these letters compared with other overprescribing letters.[24,36,37] The effects were smaller and shorter-lived for nursing home patients. It is possible that behavioral symptoms were more severe among patients in nursing homes,[38] improving the benefit-harm trade-off of antipsychotics. In addition, prescribing in nursing homes may depend on both PCP-level and nursing home–level factors,[21] diminishing the effect of a PCP-directed intervention. This concern highlights the potential value of coordinating interventions with nursing homes to ensure that their effects endure.

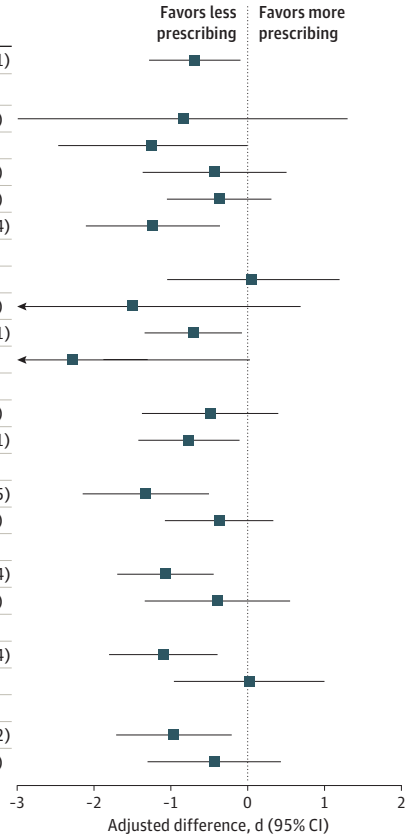
There are longstanding inequities in the quality of nursing and dementia care, particularly by race.[39-41] The subgroup analyses establish that among patients living in the community, this intervention promoted broad deprescribing across racial and ethnic groups. Effects were also similar by dual eligibility status, which can serve as a proxy for income.

Among nursing home patients, the statistical power to detect differences in effects across groups was more limited, and observed differences by race and ethnicity and dual eligibility were more difficult to discern from statistical noise. In the nursing home setting, facility-level effects may also play a role in such differences. Because of power considerations, our analyses of intervention effects by race and dual eligibility status did not distinguish within-nursing home effect heterogeneity and between-nursing home effect heterogeneity.

Figure 2. Effect of the Intervention on Quetiapine Receipt in Patient Subgroups

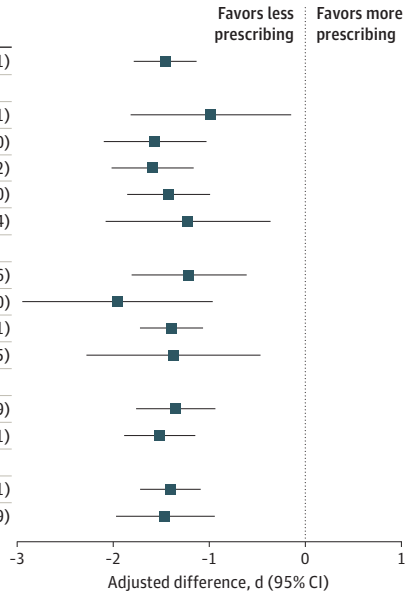
A Nursing home patients

Category	No. patient-periods	Adjusted difference, d (95% CI)	P for interaction
All	299729	-0.7 (-1.3 to -0.1)	
Age, y			.35
<65	19042	-0.8 (-3.0 to 1.3)	
65-74	46266	-1.3 (-2.5 to 0)	
75-84	90881	-0.4 (-1.4 to 0.5)	
85-94	115766	-0.4 (-1.1 to 0.3)	
≥95	27774	-1.2 (-2.1 to -0.4)	
Race and ethnicity			.20
Black	44716	0.1 (-1.0 to 1.2)	
Hispanic/Latino	19310	-1.5 (-3.7 to 0.7)	
White	225769	-0.7 (-1.3 to -0.1)	
Other	9934	-2.3 (-4.6 to 0)	
Sex			.57
Male	85370	-0.5 (-1.4 to 0.4)	
Female	214359	-0.8 (-1.4 to -0.1)	
Dual eligible			.06
Nondual	94437	-1.3 (-2.1 to -0.5)	
Dual	205292	-0.4 (-1.1 to 0.3)	
NH antipsychotic prescription			.23
≤Median	148193	-1.1 (-1.7 to -0.4)	
>Median	148150	-0.4 (-1.3 to 0.6)	
NH inspection rating			.06
≤Median	196416	-1.1 (-1.8 to -0.4)	
>Median	100088	0 (-1.0 to 1.0)	
NH staffing rating			.35
≤Median	189294	-1.0 (-1.7 to -0.2)	
>Median	104491	-0.4 (-1.3 to 0.4)	



B Community-dwelling patients

Category	No. patient-periods	Adjusted difference, d (95% CI)	P for interaction
All	965510	-1.5 (-1.8 to -1.1)	
Age, y			.66
<65	67929	-1.0 (-1.8 to -0.1)	
65-74	174946	-1.6 (-2.1 to -1.0)	
75-84	344248	-1.6 (-2.0 to -1.2)	
85-94	326710	-1.4 (-1.9 to -1.0)	
≥95	51677	-1.2 (-2.1 to -0.4)	
Race and ethnicity			.65
Black	95247	-1.2 (-1.8 to -0.6)	
Hispanic/Latino	123634	-2.0 (-2.9 to -1.0)	
White	681300	-1.4 (-1.7 to -1.1)	
Other	65329	-1.4 (-2.3 to -0.5)	
Sex			.45
Male	320335	-1.3 (-1.8 to -0.9)	
Female	645175	-1.5 (-1.9 to -1.1)	
Dual eligible			.85
Nondual	559081	-1.4 (-1.7 to -1.1)	
Dual	406429	-1.5 (-2.0 to -0.9)	



Forest plots show effects of the intervention on quetiapine receipt (measured in days) for patient subgroups. See eFigures 2-4 in Supplement 2 for subgroup results on cognitive, behavioral, and physical health end points. The first row shows the effect for the full sample (Table 3). In panel A, the final 3 subgroup analyses divide the sample according to indicators at the patient's nursing home (NH), including its antipsychotic prescribing rate, its safety inspection star rating, and its staffing rating. Sample size is given in patient-periods. Sample sizes for NH subgroup analyses do not add to total because NH indicators were not available for a small number of facilities. Error bars show 95% CIs. Bars are truncated at the limits of the x-axis scale to improve visualization of effect differences. Truncation is indicated by arrowhead at end of bar. Interaction *P* values are given for the null hypothesis that effects were equal across the subgroups. Other race/ethnicity refers to American Indian/Alaska Native, Asian/Pacific Islander, other, and unknown.

Encouragingly, the intervention appeared to reduce quetiapine prescribing at nursing homes with poorer preintervention star ratings and did so without signals of harm. Although other studies[20,21] have suggested that antipsychotics may sometimes be prescribed in lieu of adequate staffing, these results suggest that facilities with less staffing still have opportunities to safely deprescribe. These findings also point to the possibility that the intervention had similar effects across patient groups within a nursing home, but that effects differed between facilities.

We note 2 considerations for the generalizability of this work. One is that health impacts of the intervention may differ for patient groups outside the scope of our study for whom the use of antipsychotics is backed by strong evidence, including patients with serious mental illnesses who often benefit greatly from these medications. Second, the future value of this approach depends on whether physicians would react similarly to ongoing warning letters sent by other stakeholders.

Limitations

There are several limitations to this study. First, we did not directly observe administration of quetiapine and instead proxied for it with prescription drug fills. Second, we could not observe results for people enrolled in Medicare Advantage. Third, the claims-based and assessment-based outcomes might have been subject to measurement error and, in some cases, underascertainment of diagnoses.[42,43]

Conclusions

A letter intervention targeting high-volume primary care physician prescribers of quetiapine reduced receipt of this medication among their patients with dementia without detectable adverse health impacts. Our results highlight the value of simple deprescribing interventions for clinicians, specialty societies, and regulators seeking to improve the quality of dementia care. Related interventions could promote guideline-concordant care more broadly.

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SUPPLEMENT 1.

Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.

eFigure 1. CONSORT Flow Diagram of PCPs and Their Patients in Study
eFigure 2. Effect of the Intervention on Nursing Home Assessment Outcomes in Patient Subgroups
eFigure 3. Effect of the Intervention on Claims-Based Outcomes in Nursing Home Patient Subgroups
eFigure 4. Effect of the Intervention on Claims-Based Outcomes in Community-Dwelling Patient Subgroups
eTable 1. Effect of the Intervention During the First Six Quarters for Nursing Home Patients
eTable 2. Effect on Other Prescribing Outcomes
eTable 3. Effect on Alternative Measures of Cognitive, Behavioral, and Mental Health
eTable 4. Effect on Additional Utilization Outcomes

SUPPLEMENT 3.

Data Sharing Statement