

# **Peer Comparison Letters for High Volume Primary Care Prescribers of Quetiapine in Older and Disabled Adults: A Randomized Clinical Trial**

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## **Key Points**

**Question:** Can behavioral “nudges” reduce inappropriate prescribing of antipsychotics and raise clinical quality for older and disabled patients who often receive these drugs?

**Findings:** A peer comparison message randomized across the 5,055 highest Medicare prescribers of the antipsychotic quetiapine reduced prescribing for at least 2 years. Effects were larger than those observed in existing large-scale behavioral interventions, potentially due to the content of the peer comparison message, which mentioned the potential for a review of prescribing activity.

**Meaning:** Behavioral “nudge” interventions can raise the quality of prescribing, but research is still needed on how to most precisely target unsafe prescribing behavior.

## Abstract

**Importance:** Antipsychotics such as quetiapine are frequently overprescribed for indications not supported by clinical evidence, potentially causing harm.

**Objective:** Determine if peer comparison letters targeting high-volume primary care quetiapine prescribers meaningfully reduce their prescribing.

**Design, Setting and Participants:** Randomized, controlled evaluation conducted in 2015-2017 of prescribers and their patients nationwide in the Medicare program. The trial targeted the 5,055 highest-volume primary care prescribers of quetiapine in 2013-2014 (approximately 5% of all primary care quetiapine prescribers).

**Interventions:** Prescribers were randomized (1:1 ratio) to receive a placebo letter or 3 peer comparison letters stating that their quetiapine prescribing was high relative to their peers and was under review by Medicare.

**Main Outcomes and Measures:** Primary outcome was total quetiapine days supplied by prescribers from intervention start to 9 months. Secondary outcomes included quetiapine receipt from all prescribers by baseline patients, quetiapine receipt by patients with “guideline concordant” or “low value” indications for therapy, mortality and hospital utilization. In exploratory analyses, we followed outcomes to 2 years.

**Results:** Of the 5,055 prescribers, 18% were female; 5% were general practitioners, 48% were in family medicine, and 47% were in internal medicine. All were included in the analyses. Over 9 months, the treatment group supplied 11.1% fewer days of quetiapine per prescriber versus the control group (2,456 vs. 2,864 days, respectively, adjusted difference -318.7 days, 95%CI: -374.4 to -263.0,  $P<0.001$ ), which persisted through 2 years (15.6% fewer days supplied in treatment vs. control, 95%CI: -18.1% to -13.0%,  $P<0.001$ ). At the patient level, individuals in the treatment group received 3.9% (95%CI: -5.0% to -2.9%,  $P<0.001$ ) fewer days supply of quetiapine from all prescribers over 9 months, with a larger decrease among patients with “low value” vs. guideline concordant indications (5.9% vs. 2.4%, respectively;  $P=0.01$  for test that effects were equal for both groups). There was no evidence of substitution to other antipsychotics, and 9 month mortality and hospital utilization were similar between treatment vs. control groups.

**Conclusions and Relevance:** Peer comparison letters caused substantial and durable reductions in quetiapine prescribing with no evidence of negative impacts on patients.

**Trial registration:** ClinicalTrials.gov number NCT02467933.

Every year, millions of older adults are prescribed atypical antipsychotics for “off-label” use beyond the indications approved by the US Food and Drug Administration (FDA, which are limited to schizophrenia, bipolar disorder and some cases of depression).<sup>1</sup> Off-label prescribing to older adults for other indications such as behavioral symptoms in dementia, anxiety, and insomnia has continued<sup>2–4</sup> despite a large body of evidence that atypical antipsychotics are associated with significant harm in these populations.<sup>5–9</sup> These harms include a host of adverse outcomes, such as increased risk of death, cognitive decline, extrapyramidal symptoms and sedation.<sup>7,10–12</sup>

This evidence has contributed to a broad consensus among psychiatric experts that excessive off-label use of antipsychotic medications in older adults, particularly those with dementia, is a serious problem. Multiple “Choosing Wisely” recommendations from the American Psychiatric Association target off-label use of antipsychotics.<sup>13</sup> The FDA has warned against the use of antipsychotics for the treatment of elderly individuals with dementia.<sup>14</sup> The American Geriatrics Society recommends that these drugs be used only when other interventions have failed and the patient threatens self-harm or harm to others.<sup>15</sup>

Quetiapine is an atypical antipsychotic that is prescribed at a particularly high frequency for off-label use. In the US, 2.8 million patients fill a prescription for quetiapine annually,<sup>16</sup> but as much as 75% of quetiapine prescribing lacks a basis in clinical evidence, making it an attractive target for interventions to reduce off-label prescribing.<sup>17</sup>

The widespread off-label use of antipsychotics in spite of clear guidelines has attracted the attention of CMS and federal oversight agencies.<sup>2,18</sup> However, there is a gap between the need to curb antipsychotic overprescribing and the evidence base of effective interventions to change prescriber behavior. One existing approach focuses on changing providers’ beliefs about

the clinical benefits of prescribing; this intensive provider education can raise the quality of psychiatric medication prescribing.<sup>19,20</sup> Another set of techniques based on behavioral economics involves harnessing peer comparison messaging to “nudge” physicians to change behavior without financial incentives.<sup>21–26</sup> Yet there is limited evidence on bringing provider education or behavioral nudges to a national scale. To our knowledge, no large scale randomized behavioral interventions have targeted antipsychotic prescribing.

We performed a randomized, controlled evaluation of peer comparison letters to high quetiapine-prescribing primary care physicians with the goal of reducing excessive prescribing among Medicare beneficiaries. Because peer comparison letters are relatively inexpensive and easily scaled, they could be a powerful approach to improve the safety of antipsychotic prescribing.

## **METHODS**

### **Study Design and Participants**

The study used a placebo-controlled, parallel group design with balanced (1:1) randomization to the treatment (peer comparison letter) and control (placebo letter) groups. It was overseen by an interdisciplinary team at the Center for Medicare and Medicaid Services (CMS), the US Office of Evaluation Sciences, as well as institutional review boards at the Massachusetts Institute of Technology, Harvard University, and Columbia University.

Study participants were primary care providers, or prescribers, (PCPs) chosen by a CMS analysis of quetiapine prescribing in Medicare Part D (prescription drug coverage) from 2013 to 2014. We chose PCPs (prescribers with a specialty of “general practice,” “family practice,” or “internal medicine”) because the lack of psychiatric specialization suggested less formal training

in prescribing of antipsychotics. We defined quetiapine prescriptions as prescriptions for branded Seroquel, Seroquel XR, or generic quetiapine.

Power calculations indicated that a sample of  $N=5,000$  would have 80% statistical power to detect an intervention effect of 1.5%-1.7% on overall prescribing at the 5% significance level. Study participants were identified from the pool of PCPs with at least 10 quetiapine prescriptions in 2013 and 2014 who prescribed significantly more quetiapine than other such prescribers in their state. PCPs were classified as high prescribers if their prescribing was  $\geq 75^{\text{th}}$  percentile plus a multiplier factor of the interquartile range versus other PCPs in the same state (a modified Tukey outlier method) on two measures of quetiapine prescribing.<sup>27</sup> These measures were 1) the number of quetiapine prescription fills dispensed and 2) the total days supply of quetiapine dispensed, regardless of the number of patients (Supplement 1). A multiplier factor of  $\frac{1}{4}$  identified 5,055 prescribers (roughly 5% of all PCP quetiapine prescribers) exceeding the outlier threshold for both measures in 2013 and 2014, which met our power calculations and became the study sample.

## **Intervention**

The intervention was a mailed peer comparison letter using social norms from the Center for Program Integrity within CMS on PCPs' quetiapine prescribing behavior.<sup>23</sup> Its message and format drew upon insights from previous randomized evaluations of letter interventions.<sup>25,28,29</sup> The letter (Supplement 1) indicated that the prescriber's quetiapine prescribing was under review by CMS and was extremely high relative to their within-state peers. The text of the letter discussed that high quetiapine prescribing could be appropriate but was concerning for medically unjustified use. The letter encouraged PCPs to review their prescribing patterns and explained that PCPs could expect to receive future communications from CMS. The placebo intervention

was a letter and pamphlet discussing an unrelated Medicare provider enrollment regulation, sent to allow CMS to observe whether letters were returned to sender in the full sample.

Intervention and placebo letters were mailed in April 2015. Drawing on literature that has found the effects of letters to grow when they are sent repeatedly, two follow-up intervention letters with more recent prescribing data were sent in August and October 2015 to treatment arm prescribers.<sup>30</sup> An additional notice was sent to the control arm in June 2015 clarifying the enrollment process and the regulation.

The trial ended after the second follow-up letter upon CMS's request that the study team report the effect of the intervention. The pre-specified analysis plan was finalized in March 2016 and researchers were then un-blinded to the post-intervention data.

## **Randomization**

Prescribers were allocated by the first study author to treatment and control arms using a random sequence of numbers and a pre-specified re-randomization procedure (Supplement 1).

## **Data Sources**

We analyzed prescribers and patients using 100% Medicare claims data from 2013-2017, enrollment data from 2015-2017, and risk-adjustment data from 2013 and 2014. Data were analyzed using Stata/MP version 13.

## **Prescriber and Patient-Level Outcomes**

The primary outcome was measured at the prescriber level and pre-specified as the cumulative total days of quetiapine supplied by PCPs in the 9 months following the intervention start (the initial mailing of letters). This outcome measure counts the number of quetiapine fills at pharmacies paid by Medicare Part D that were attributed to the targeted prescriber, quantified using the total days supply of the fills. We chose total days supply to integrate both changes in

supply to continuing patients and initiations to new patients. As an exploratory outcome, we also assessed days supplied over an extended duration of 2 years.

We pre-specified several additional secondary outcomes at the prescriber and patient level; we highlight several here and provide the full set in Supplement 1. At the prescriber level, we additionally examined new quetiapine starts by PCPs, defined as all quetiapine days supplied to patients who had not received quetiapine prescription from the study PCP during the last year. We also examined possible substitution towards similar “atypical” antipsychotic medications, the same drug class as quetiapine, as well as other psychiatric medications.

For patient level outcomes, we defined a baseline cohort of patients as those receiving quetiapine from any study prescriber in the year prior to the intervention (characteristics in **Table 1**, see Supplement 1 for more details). For this cohort, we examined the number of quetiapine fills over 9 months and 2 years, measured in days supply from *all prescribers*, divided into three mutually exclusive sources: the patient’s baseline study prescriber, other psychiatric prescribers, and other non-psychiatric prescribers. We further examined health care utilization after the intervention including inpatient admissions, emergency department visits, and psychiatrist outpatient visits, all cumulative to 9 months.

Across several outcomes, we also assessed the effect of the intervention based on the likely indication for quetiapine prescribing. We defined two cohorts of patients, those with FDA approved indications (“guideline-concordant” prescribing) and those whose indications likely fall under the FDA’s quetiapine black box warning (“low-value” prescribing),<sup>14,31</sup> which also aligns with existing clinical guidelines.<sup>15</sup> Using pre-intervention diagnoses from 2013-2014, quetiapine prescribing for patients with bipolar disorder, schizophrenia, or major depression without dementia or Alzheimer’s disease was deemed “guideline-concordant,” whereas



prescribing to patients with dementia or Alzheimer's disease but none of the major psychiatric illnesses above was considered "low-value" (**eTable 1** in Supplement 2). Patients in the guideline-concordant and low-value groups comprised 29% and 26% of the total baseline patient cohort, respectively (**Table 1** and **eTable 2** in Supplement 2). The residual group was composed of patients with no history of either category of diagnoses or with a history of diagnoses in both categories (Supplement 1); exploratory analyses of this group showed effects similar to the overall effects.

### **Statistical Approach**

We used multivariable linear regression models to evaluate the effect of the intervention. To increase the statistical power of our analyses, we pre-specified multivariable adjustment for the level of the outcome prior to the start of the intervention and for several additional characteristics (Supplement 1).<sup>32,33</sup> We used robust variance techniques in all statistical models, and patient-level analyses accounted for intra-prescriber correlation with clustering at the prescriber level. Two-sided hypothesis tests with  $P < 0.05$  were considered significant. To facilitate comparisons of outcomes with different levels, in some analyses we estimated a percent effect by dividing the absolute effect (e.g. absolute difference in quetiapine days supplied) and confidence interval by the control group mean outcome.

### **RESULTS**

Of the 5,055 study prescribers, 2,528 were allocated to the control arm (placebo letter) and 2,527 prescribers were allocated to the treatment arm (peer comparison letters). Two prescribers were not sent follow-up letters because they had died. All 5,055 prescribers were included in analyses (**Figure 1**). The baseline patient cohort contained 89,500 patients, 43,911

aligned to the treatment arm and 45,589 aligned to the control arm (**Table 1** and **eFigure 1** in Supplement 2).

The average prescriber in the study was responsible for supplying 2,916.0 days (97.2 months) of quetiapine during the 9 months before the intervention, or about 3 months of quetiapine prescribed per week. 820.3 (28%) of these days, on average, were to patients for likely “low-value” indications and 777.6 (27%) were to patients with likely “guideline-concordant” indications. The average baseline patient received 192.6 days (6.4 months) of quetiapine during the 9-month pre-intervention period.

### **Prescriber-Level Outcomes**

During the 9 month post-intervention period, the average treatment group prescriber supplied 2,455.8 days (81.9 months) of quetiapine vs. 2,864.0 days (95.5 months) in the control group, a reduction of 318.7 days per prescriber (adjusted difference; 95% CI, 263.0-374.4), or an 11.1% decrease versus control (95% CI, 9.2%-13.1%,  $P<0.001$ ; **Table 2** and **Figure 2A**).

Extending the post-intervention period to 2 years, the cumulative effect was a 15.6% relative decrease versus control (95% CI 13.0%-18.1%,  $P<0.001$ ). The intervention was also associated with a significant decrease of 27.1% relative to control (95% CI 23.1%-31.1%,  $P<0.001$ ; **Table 2** and **Figure 2B**) in the volume of new quetiapine prescriptions over 9 months, which also persisted cumulative to 2 years (24.3% relative decrease, 95% CI 20.6%-28.0%,  $P<0.001$ ).

At the prescriber level, the intervention reduced quetiapine prescribing to both low-value and guideline-concordant patients (**Table 2** and **eFigure 2A** in Supplement 2). There was a smaller decrease in prescribing to guideline-concordant patients, though the effect was not statistically different when compared to the decrease for low-value patients ( $P=0.25$  over 9 months and  $P=0.17$  cumulative to 2 years).

## Patient-Level Outcomes

We additionally examined quetiapine prescribing at the patient-level – i.e., how the intervention affected the average baseline patient’s receipt of quetiapine from all prescribers over the outcome period. The intervention was associated with a reduction of 6.7 days of quetiapine received per patient over 9 months (95% CI 4.9-8.5,  $P<0.001$ ), or a 3.9% relative decrease (95% CI 2.9%-5.0%,  $P<0.001$ ; **Table 2**). The cumulative effect at 2 years grew to a 5.6% relative decrease (95% CI 4.3%-6.8%,  $P<0.001$ ).

There was a significantly smaller reduction in receipt of quetiapine for guideline-concordant patients than for low-value patients ( $P=0.01$  for difference in percent reduction between the two patient groups both over 9 months and cumulative to 2 years; **Table 2** and **eFigure 2B** in Supplement 2). For low-value patients, the intervention was associated with a 5.9% reduction in quetiapine receipt over 9 months (95% CI, 3.9%-8.0%,  $P<0.001$ ), and a larger 7.9% decrease cumulative to 2 years (95% CI 5.4%-10.4%,  $P<0.001$ ). An exploratory analysis showed that the entirety of this effect came from the study prescribers, with no compounding or offsetting change from other (non-baseline) prescribers (**Figure 3A**).

For guideline-concordant patients, there was a relative reduction of 2.4% over 9 months (95% CI, 0.9%-4.0%,  $P=0.002$ ) and 4.0% over 2 years (95% CI 2.3%-5.7%,  $P<0.001$ ) in quetiapine receipt. In exploratory analyses, we found that 40% of the reduction for guideline-concordant patients from study physicians was offset by shifting prescriptions to other prescribers (**Figure 3B**). Most of the offset was due to an increase in quetiapine receipt from other (non-baseline) physicians with psychiatric specialization (the remainder came from other providers: study prescribers from whom the patient did not previously receive quetiapine, and non-psychiatric prescribers outside the study).

To test for effects on total cessation of quetiapine, we considered whether patients received any quetiapine in each quarter (exploratory; **eFigure 3** in Supplement 2). Percent effects on total cessation were roughly twice as large for low-value patients as for guideline-concordant patients.

There was no statistically significant impact of the intervention on PCP supply or patient receipt of other antipsychotics, anti-anxiety drugs, sleep aids, and antidepressants (**eTables 4 and 5** in Supplement 2). We explored receipt of all antipsychotics for the low-value and guideline-concordant patient subgroups (exploratory; **eTable 6** in Supplement 2). While both subgroups experienced increases in receipt of other antipsychotics, the magnitudes were small, leaving the qualitative impact of the intervention on total receipt unchanged.

There was no significant change in mortality, inpatient admissions, ED visits or psychiatrist visits for baseline patients during the 9 month outcome period; exploratory analyses of the patient subgroups detected only a reduction in ED visits for guideline-concordant patients (**eFigure 4** in Supplement 2).

## DISCUSSION

In this randomized, controlled evaluation we found that peer comparison letters targeting the 5,055 highest quetiapine prescribing physicians in the Medicare program led to statistically significant, persistent decreases in quetiapine prescribing. The decrease was pronounced for new quetiapine prescribing, suggesting a particular impact on physicians' decision making over whether to initiate quetiapine treatment. The intervention was associated with reductions in prescribing to both guideline-concordant and low-value patients at the prescriber level, but at the patient level, low-value patients had a significantly greater decline in quetiapine receipt. We detected no adverse impacts in care utilization and mortality data. These results provide

encouraging evidence that high prescribers of antipsychotics can decrease quetiapine prescribing without adverse clinical consequences in response to a letter highlighting their overall high rates of prescribing.

In comparison to existing work on prescribing quality, this study provides a unique example of a large-scale intervention yielding clinically meaningful, persistent effects. For example, a recent antibiotic prescribing “nudge” targeting general practitioners throughout England reduced inappropriate prescribing by 3.3%.<sup>24</sup> Effects were smaller than those of recent promising behavioral interventions on prescribing that targeted a more limited number of providers (where, for example, a peer comparison message reduced inappropriate antibiotic prescribing by 22% and effects endured post-intervention), though those interventions involved more complex changes like modifying electronic health record systems.<sup>22,23,34</sup>

The findings also contrast to the null effect of a similar intervention performed by members of this study team targeting high prescribers of controlled substances, including opioids.<sup>25</sup> This study incorporated lessons from that work that could have contributed to the more substantial effect we observed. First, it targeted a wider range of high prescribers, approximately 5% of quetiapine prescribing PCPs, versus the top 0.3% of all Schedule II controlled substance prescribers in the previous study. Second, the letters in this study had stronger wording around the possibility that prescribing was inappropriate and could be reviewed which may have led physicians to take it more seriously. This finding can guide future evaluations of randomized letters with a variety of framings to find optimally effective approaches to communication.

Encouragingly, in many domains, we did not observe evidence consistent with significant unintended consequences from this intervention, such as substitution away from quetiapine towards another antipsychotic medication. On the other hand, we did observe reductions in the

receipt of quetiapine among guideline-concordant patients, which could represent negative effects from PCPs cutting quetiapine use indiscriminately, even for patients who may need it. If this represented a harmful change for patients, we may have expected to see higher rates of adverse outcomes in the guideline-concordant group as prescribing rates decreased. However, if anything, guideline-concordant patients experienced lower rates of hospital encounters after the intervention. Though there are negative outcomes beyond these that we may not observe, these results suggest that PCPs may be able to target “guideline concordant” patients for whom stopping quetiapine may be clinically justifiable while maintaining access for patients who experience clinical benefits (by continuing to prescribe to these patients or by shifting them to psychiatrists). In future interventions, it will be important to specifically target low-value care, for example by selecting physicians not just by their high overall prescribing, but by their high rates of low-value prescribing.

This study has several limitations. First, our analysis included only prescribing covered by Medicare Part D. The letters may have encouraged physicians to reevaluate their prescribing to patients with private insurance, Medicaid, or no insurance coverage. This “spillover” effect could amplify or dampen the magnitude our findings, depending on the nature of the spillovers. A second limitation concerns the external validity of the study, were it to be scaled or repeated in a different population. The letters’ effectiveness may have come from their novelty, and the magnitude of effects may decline if letters are used frequently or across multiple settings (e.g. antibiotics, opioids, benzodiazepines), similar to the well-documented phenomenon of “alert fatigue”. Letters sent to other populations, like prescribers who were not high-volume outliers, could have different effects. Third, we classify guideline-concordant and low-value prescribing using administrative data which may have measurement error. Validation studies would enable

future interventions to use this data more confidently. Fourth, our outcomes did not measure quality of life or mental health directly, which may have been the most likely domains for detecting a negative effect if the intervention caused harm.

Finally, due to limitations in data access, we could not estimate effects for patients who were classified as neither guideline-concordant nor low-value. Imputed effects for this group were similar to overall effects, but we do not report them because it was not possible to impute confidence intervals. We also were not able to assess the characteristics of the psychiatric (and non-psychiatric) providers who offset reductions in quetiapine prescribing by study providers.

In conclusion, we found that a low-cost series of letters targeting PCPs who were high prescribers of quetiapine in the Medicare program resulted in large, sustained decreases in prescribing. We observed greater decreases in likely low-value, off label prescribing than in potentially guideline-concordant prescribing with little evidence of “gaming” by providers or negative impact on patients. With increasing awareness of the dangers of inappropriate prescribing, this study provides evidence that peer comparison letters targeted at high-risk medications could effectively and efficiently create durable improvements in prescribing patterns.

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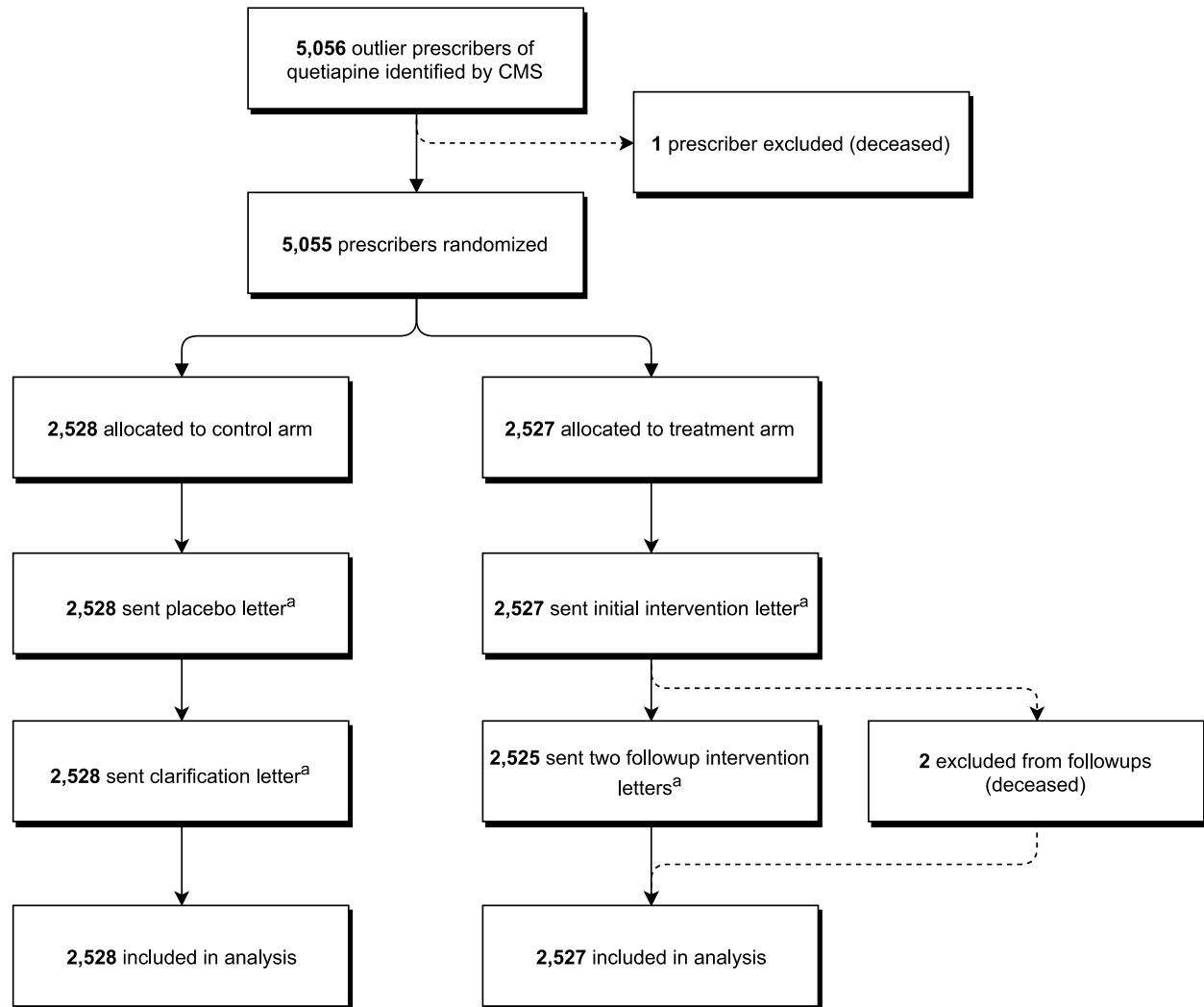
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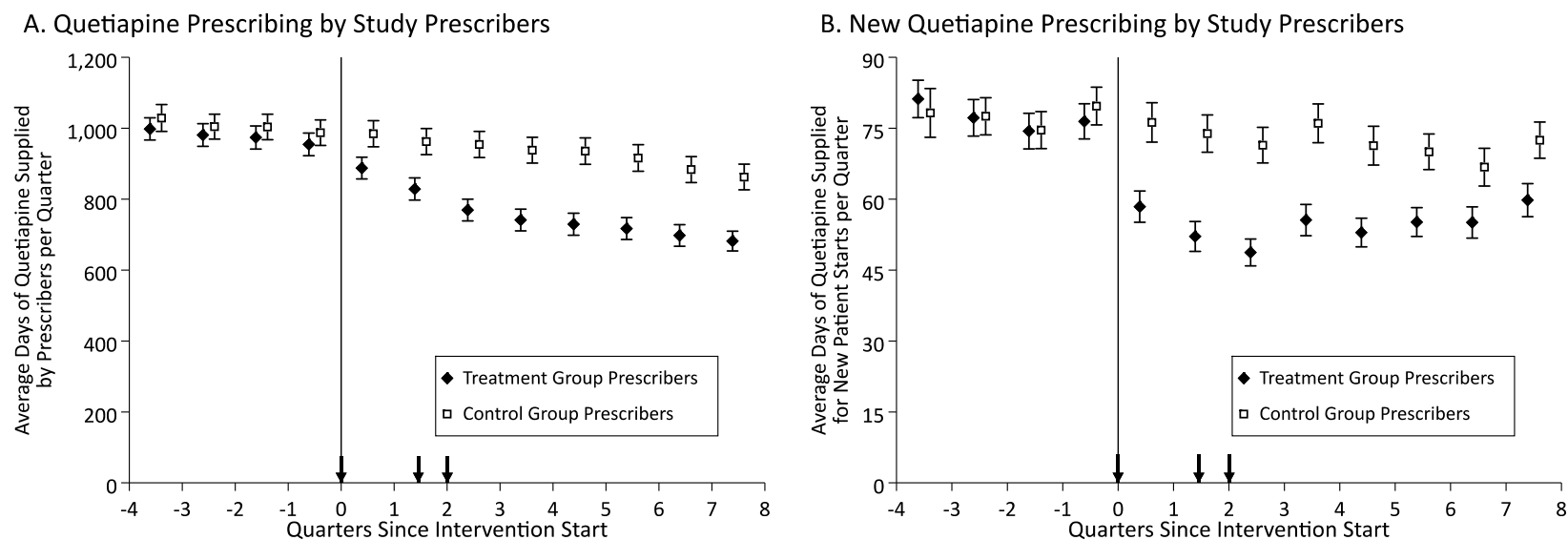
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**Figure 1: CONSORT Flow Diagram of Prescribers in Study**



<sup>a</sup> Reproductions of letters can be found in Supplement 1.

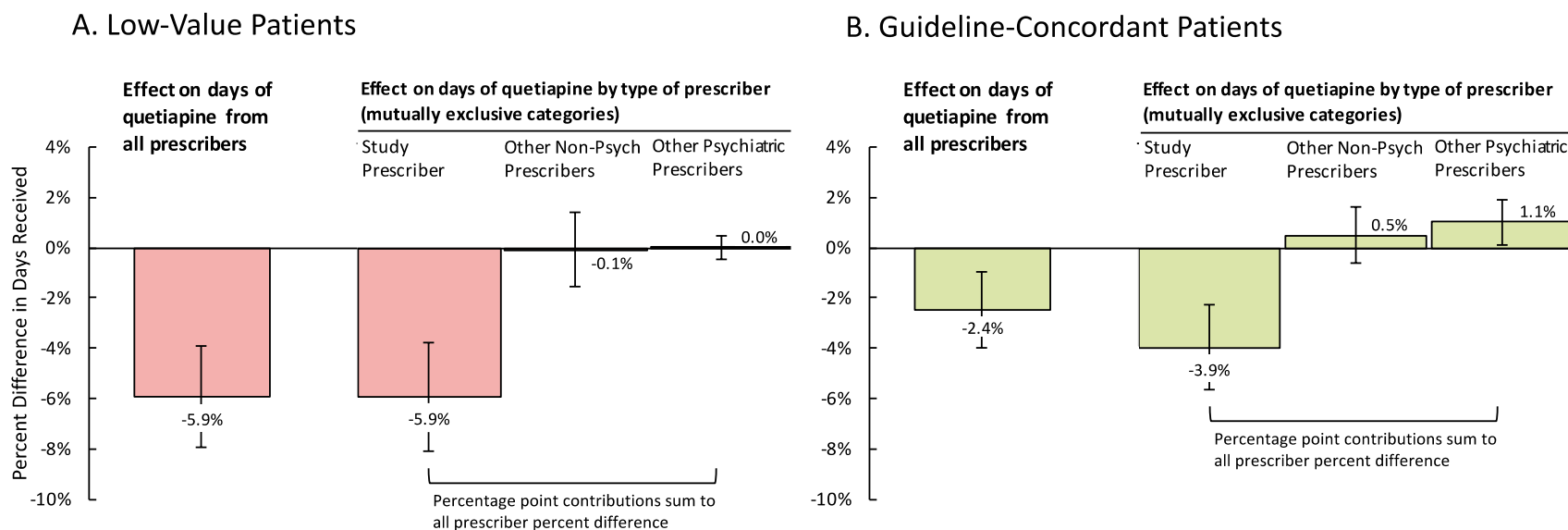
**Figure 2: Quarterly Average Quetiapine Prescribing in Treatment and Control Groups**



Each point represents the average days of quetiapine supplied in each quarter per prescriber relative to the intervention start date.

Panel A counts all days supplied by the prescribers and Panel B counts only days supplied for new patient starts. Error bars indicate 95% CIs. Arrowheads denote when letters were sent to prescribers.

**Figure 3: Cumulative Effect on Receipt of Quetiapine by Low-Value and Guideline-Concordant Patients over 9 Months**



In each panel, leftmost bar shows the percent difference in days of quetiapine between treatment and control patients from all prescribers in the 9 months after the start of the intervention. Next three bars display percentage point contributions to the percent difference of three mutually exclusive categories: the patient's study prescriber, other non-psychiatric prescribers, and other psychiatric prescribers. The contributions of these three categories sum to the all prescriber percent difference. Panel A displays this breakdown for low-value patients and Panel B displays it for guideline-concordant patients. Each bar reports an adjusted percent difference (difference between treatment and control means, adjusting for baseline receipt and other characteristics described in text and Supplement 1, divided by the control mean). Error bars indicate 95% CIs. See **eTable 3** in Supplement 2 for coefficients.

**Table 1: Characteristics of Study Participants at Baseline\***

<b>Characteristics of Prescribers</b>	<b>Control (N=2,528)</b>	<b>Treatment (N=2,527)</b>
Quetiapine Days Supplied (9 Month Baseline Period)		
To All Patients	2,960±2,669	2,872±2,401
To New Patients	229±260	225±243
To Low-Value Patients	846±1,307	794±1,250
To Guideline-Concordant Patients	786±924	769±798
Prescriber Enrolled to Bill Original Medicare <sup>a</sup>	1,745 (69.0)	1,784 (70.6)
Female Sex <sup>a</sup>	447 (17.7)	453 (17.9)
Specialty <sup>a</sup>		
General Practitioner	104 (4.1)	127 (5.0)
Family Medicine	1,186 (46.9)	1,242 (49.1)
Internal Medicine	1,238 (49.0)	1,158 (45.8)
<b>Characteristics of Baseline Patients</b>		
Number of Patients	45,589	43,911
Number of Patients, by Group		
Low-Value	12,105	11,385
Guideline-Concordant	13,050	12,630
Quetiapine Days Received (9 Month Baseline Period)	193±118	192±117
Quetiapine Days Received, by Group <sup>b</sup>		
Low-Value, 26% of patients	191±116	189±116
Guideline-Concordant, 29% of patients	202±118	203±115
Age	70.4±16.2	70.3±16.2
Nonwhite Race <sup>a</sup>	13,415 (29.4)	13,200 (30.1)
Female Sex <sup>a</sup>	29,144 (63.9)	27,963 (63.7)
Dementia or Alzheimer's <sup>a</sup>	20,790 (45.6)	19,558 (44.5)
Major Psychiatric Illness <sup>a</sup>	21,735 (47.7)	20,803 (47.4)
Institutionalized in a Long-Term Care Facility <sup>a</sup>	7,178 (15.7)	6,468 (14.7)
Qualifies for Medicare by Disability <sup>a</sup>	17,028 (37.4)	16,315 (37.2)
Dual Medicare-Medicaid Eligible <sup>a</sup>	27,222 (59.7)	26,158 (59.6)

\* Plus-minus values are means ± standard deviations. All means of days supplied/received refer to quetiapine fills in the baseline period, the 9 months before the intervention began. The only significant difference in baseline characteristics between the groups was in prescriber specialty ( $P=0.044$ ). The sample was the 5,055 study prescribers (prescriber rows) and 89,500 patients (patient rows).

<sup>a</sup> Number of observations (percent of observations)

<sup>b</sup> The low-value and guideline-concordant patient shares do not sum to 100% because they exclude patients who carried both low-value and guideline-concordant diagnoses (19% of baseline patients), neither a low-value nor a guideline-concordant diagnosis (24% of patients), or no diagnosis data in 2013-2014 (2% of patients).

**Table 2: Effect of Intervention on Primary and Key Secondary Outcomes\***

	Cumulative Total Quetiapine Days over 9 Months							
	N <sup>a</sup>	Control Mean	Treatment Mean	Difference (95% CI)	P Value	Adjusted Difference (95% CI) <sup>b</sup>	Percent Difference (95% CI) <sup>c</sup>	P Value
<b>Prescribers: Quetiapine Days Supplied per Prescriber</b>								
To All Patients	5,055	2,864	2,456	-408 (-548 to -268)	<0.001	-319 (-374 to -263)	-11.1% (-13.1% to -9.2%)	<0.001
To New Patients	5,055	219	157	-62 (-74 to -49)	<0.001	-59 (-68 to -50)	-27.1% (-31.1% to -23.1%)	<0.001
To Low-Value Patients	5,055	753	619	-134 (-196 to -71)	<0.001	-91 (-115 to -67)	-12.1% (-15.3% to -8.9%)	<0.001
To Guideline-Concordant Patients	5,055	753	665	-88 (-135 to -42)	<0.001	-74 (-95 to -53)	-9.8% (-12.6% to -7.1%)	<0.001
P value, low-value effect = guideline-concordant effect				0.24		0.26	0.25	
<b>Patients: Quetiapine Days Received Per Patient</b>								
All Patients	89,500	169.7	162.9	-6.8 (-10.3 to -3.2)	<0.001	-6.7 (-8.5 to -4.9)	-3.9% (-5.0% to -2.9%)	<0.001
Low-Value Patients	23,490	158.7	147.9	-10.9 (-15.0 to -6.7)	<0.001	-9.4 (-12.6 to -6.2)	-5.9% (-8.0% to -3.9%)	<0.001
Guideline-Concordant Patients	25,680	182.1	177.9	-4.3 (-9.4 to 0.9)	0.102	-4.5 (-7.2 to -1.7)	-2.4% (-4.0% to -0.9%)	0.002
P value, low-value effect = guideline-concordant effect				0.04		0.02	0.01	
	Cumulative Total Quetiapine Days over 2 Years <sup>d</sup>							
	N <sup>a</sup>	Control Mean	Treatment Mean	Difference (95% CI)	P Value	Adjusted Difference (95% CI) <sup>b</sup>	Percent Difference (95% CI) <sup>c</sup>	P Value
<b>Prescribers: Quetiapine Days Supplied per Prescriber</b>								
To All Patients	5,055	7,436	6,052	-1,384 (-1,752 to -1,015)	<0.001	-1,157 (-1,343 to -970)	-15.6% (-18.1% to -13.0%)	<0.001
To New Patients	5,055	578	438	-140 (-173 to -108)	<0.001	-141 (-162 to -119)	-24.3% (-28.0% to -20.6%)	<0.001
To Low-Value Patients	5,055	1,801	1,401	-400 (-549 to -251)	<0.001	-306 (-379 to -233)	-17.0% (-21.0% to -13.0%)	<0.001
To Guideline-Concordant Patients	5,055	1,922	1,619	-302 (-418 to -187)	<0.001	-264 (-327 to -201)	-13.7% (-17.0% to -10.5%)	<0.001
P value, low-value effect = guideline-concordant effect				0.29		0.34	0.17	
<b>Patients: Quetiapine Days Received per Patient</b>								
All Patients	89,500	385.7	364.9	-20.8 (-29.2 to -12.3)	<0.001	-21.5 (-26.4 to -16.6)	-5.6% (-6.8% to -4.3%)	<0.001
Low-Value Patients	23,490	327.1	298.5	-28.5 (-38.0 to -19.0)	<0.001	-25.8 (-33.9 to -17.8)	-7.9% (-10.4% to -5.4%)	<0.001
Guideline-Concordant Patients	25,680	442.1	424.9	-17.2 (-30.3 to -4.2)	0.010	-17.6 (-25.1 to -10.1)	-4.0% (-5.7% to -2.3%)	<0.001
P value, low-value effect = guideline-concordant effect				0.15		0.13	0.01	

\* All outcomes count quetiapine days supplied/received cumulative to 9 months or cumulative to 2 years (as specified), beginning at the start of the intervention.

<sup>a</sup> Indicates the number of study prescribers (prescriber rows) or number of baseline patients (patient rows) included in the estimates.

<sup>b</sup> Adjusts for baseline supply/receipt and other characteristics to raise statistical power (see text and Supplement 1 for more details).

<sup>c</sup> Reports adjusted difference and confidence interval divided by the control mean.

<sup>d</sup> Exploratory extension of outcome duration.