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Citation

Law, Michael R. 2009. "Costs and Consequences of Direct-to-Consumer Advertising for Clopidogrel in Medicaid." *Archives of Internal Medicine* 169 (21) (November 23): 1969.
doi:10.1001/archinternmed.2009.320.

Published Version

doi:10.1001/archinternmed.2009.320

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HEALTH CARE REFORM

Costs and Consequences of Direct-to-Consumer Advertising for Clopidogrel in Medicaid

Michael R. Law, PhD; Stephen B. Soumerai, ScD; Alyce S. Adams, PhD; Sumit R. Majumdar, MD, MPH

Background: Direct-to-consumer advertising (DTCA) is assumed to be a major driver of rising pharmaceutical costs. Yet, research on how it affects costs is limited. Therefore, we studied clopidogrel, a commonly used and heavily marketed antiplatelet agent, which was first sold in 1998 and first direct-to-consumer advertised in 2001.

Methods: We examined pharmacy data from 27 Medicaid programs from 1999 through 2005. We used interrupted time series analysis to analyze changes in the number of units dispensed, cost per unit dispensed, and total pharmacy expenditures after DTCA initiation.

Results: In 1999 and 2000, there was no DTCA for clopidogrel; from 2001 through 2005, DTCA spending exceeded \$350 million. Direct-to-consumer advertising did not change the preexisting trend in the number of clopidogrel units dispensed per 1000 enrollees ($P = .10$). How-

ever, there was a sudden and sustained increase in cost per unit of \$0.40 after DTCA initiation (95% confidence interval, \$0.31-\$0.49; $P < .001$), leading to an additional \$40.58 of pharmacy costs per 1000 enrollees per quarter thereafter (95% confidence interval, \$22.61-\$58.56; $P < .001$). Overall, this change resulted in an additional \$207 million in total pharmacy expenditures.

Conclusions: Direct-to-consumer advertising was not associated with an increase in clopidogrel use over and above preexisting trends. However, Medicaid pharmacy expenditures increased substantially after the initiation of DTCA because of a concomitant increase in the cost per unit. If drug price increases after DTCA initiation are common, there are important implications for payers and for policy makers in the United States and elsewhere.

Arch Intern Med. 2009;169(21):1969-1974

THE COST OF DRUGS TO PUBLIC and private health insurance programs has been a long-standing source of concern among policy makers.¹ Despite slowing growth in recent years, prescription drug costs in Medicaid increased 15.4% on average annually between 1994 and 2004.² Moreover, State Medicaid directors report that prescription drugs are 1 of the top 3 reasons for overall Medicaid expenditure growth.³ The enrollment of millions of Americans in publicly funded Medicare Part D programs elevates this concern.

*See also pages 1976
and 2024*

One controversial potential driver of drug costs is direct-to-consumer advertising (DTCA).⁴ Spending for DTCA has increased more than 330% in the past 10 years.⁵ Moreover, it has been the subject of recent legislative proposals in the United States and is banned in most other countries.^{6,7} Much DTCA relates to lifestyle drugs such as those for erectile dysfunction

and insomnia; however, substantial resources are directed at cardiovascular medications such as statins, angiotensin-converting enzyme inhibitors, and antiplatelet agents such as clopidogrel. One could surmise that DTCA might lead to increased expenditures via 3 mechanisms. First, and most directly, increased use as a result of marketing directed to patients would lead to increased total pharmacy costs. Second, regardless of increased use itself, pharmaceutical companies might try to offset the expense of DTCA—almost \$5 billion in 2006⁸—by increasing the price of the advertised drug. Third, if manufacturers expect or receive an expanded indication for a particular product, they may both increase price and initiate DTCA.

*See Invited Commentary
on page 1985*

To recoup the substantial costs of DTCA, firms must generate higher revenues through increased sales, higher prices, or both.⁹ Existing research on the impact of DTCA has focused on drug ex-

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penditures¹⁰⁻¹² or use^{13,14} but not on the relationship between them. Moreover, much of the existing research on the impact of DTCA has compared drugs with different levels of advertising or with unadvertised drugs, which are both potentially prone to selection bias.^{10,15,16} As DTCA is used more extensively for drugs with larger potential patient populations,¹⁷ it is highly likely that heavily advertised medications would sell more than other drugs, even without DTCA. Another major limitation of existing research is that DTCA typically starts shortly after drugs are initially marketed. As a result, it is extremely difficult to separate the independent effect of DTCA from other drug promotion activities such as the provision of samples and direct-to-physician advertising through “detailing.” Therefore, we examined longitudinal changes in the use and cost of clopidogrel, which has been marketed extensively using DTCA starting in 2001, several years after it was initially released. This preliminary analysis of an ideal case study allowed us to estimate changes in prescribing after the initiation of DTCA, while controlling for existing pre-DTCA trends. In 2005 alone, clopidogrel was among the 10 drugs with the highest advertising expenditure, with DTCA spending estimated at \$110 million.⁵ We hypothesized that, from the perspective of large payers, such as US Medicaid, the initiation of clopidogrel DTCA would be associated with an increase in total pharmacy expenditures.

METHODS

SUBJECTS AND SETTING

We studied the impact of DTCA in Medicaid, which accounted for more than two-thirds of public expenditures on prescription drugs in 2005.² We used data from Medicaid programs from 1999 through 2005 compiled by the Centers for Medicare and Medicaid Services.¹⁸ These data contain quarterly information on the number of units dispensed and pharmacy reimbursement for clopidogrel by state. We did not use data after 2005 because many individuals who were dually eligible for both Medicaid and Medicare were transferred to Medicare Part D plans starting in 2006. Previous studies have demonstrated the validity and reliability of these data for studying prescribing interventions.¹⁹⁻²¹ We converted all costs to 2005 US dollars using the Consumer Price Index.²² To calculate utilization rates, we used state-level Medicaid enrollment data from the Centers for Medicare and Medicaid Services.²³ Specifically, we focused on Medicaid programs that reported quarterly data for the 6 years of our study and that did not have prior authorization requirements for clopidogrel. This search yielded a population-based study sample of 27 Medicaid programs (the programs analyzed included Alaska, California, Connecticut, District of Columbia, Florida, Georgia, Idaho, Illinois, Indiana, Kentucky, Louisiana, Maine, Massachusetts, Missouri, Montana, Nebraska, New Jersey, New Mexico, New York, Oregon, Rhode Island, South Carolina, South Dakota, Texas, Virginia, Washington, and Wisconsin; the only state with complete data that was not included was Oklahoma [the prior authorization requirement for clopidogrel was instituted in 2003]). Collectively, these 27 Medicaid programs covered more than 30 million Medicaid enrollees at the end of 2005, which was 16% of the total population of the 27 states and 67% of the total national Medicaid enrollment.²⁴ In 2004, enrollees in the 27 states were 59.9% female, and their race/ethnicity was

37.7% white, 22.5% African American, 27.0% Latino, and 12.8% other or unknown.²⁵

STUDY DRUG

Clopidogrel (Plavix) is a platelet aggregation inhibitor that was approved in 1997 for the treatment of acute coronary syndromes and the prevention of atherosclerosis-related events. In 2005, it was the world's second highest-selling drug, with sales of \$5.9 billion.²⁶ In 2003, Medicaid reimbursement for clopidogrel was just under \$400 million, making it Medicaid's 10th most costly drug.²⁷ No other prescription antiplatelet therapy appeared in the top 40 most costly drugs dispensed to Medicaid patients in 2003.²⁷ To determine total DTCA expenditures for clopidogrel over the study period, we used annual estimates of advertising expenditure from TNS Media Intelligence.²⁸ Also, because network news advertising is thought to be a particularly influential mode of DTCA, we calculated the number of clopidogrel commercials on national network news broadcasts on a quarterly basis using the Vanderbilt Television News Archive.²⁹

STATISTICAL ANALYSIS

Our primary analysis used interrupted time series analysis, one of the strongest quasi-experimental designs, to examine longitudinal changes in trends of clopidogrel use and cost.³⁰ We examined 3 outcomes. First, to assess changes in trends of clopidogrel use before and after DTCA initiation, we examined the number of units per 1000 Medicaid enrollees per quarter. Clopidogrel was available in only 1 unit size (75 mg) during the study period, providing a consistent measure of population-level drug use over time. This unit size is equivalent to the defined daily dose of clopidogrel.³¹ Second, to examine possible changes in pricing, we examined pharmacy costs per unit of clopidogrel per quarter. Finally, for our main outcome, we examined total Medicaid reimbursed costs for clopidogrel per 1000 Medicaid enrollees in each quarter.

Our time series analysis estimated any immediate changes in the level or changes in the long-term trend of the use and cost outcomes after the start of DTCA, while simultaneously controlling for existing pre-DTCA trends in use.³⁰ As clopidogrel was available and widely used in Medicaid programs for several years before DTCA, initial marketing activities and initial uptake and diffusion should not be potential confounders in the analysis. Clopidogrel DTCA started in 2001, and the first national network news exposure documented in the Vanderbilt database was in December 2001 (see the “Results” section). Therefore, we analyzed all models using the fourth quarter of 2001 as the start date for DTCA, and we excluded this quarter from all models because DTCA started during this observation period. We used a generalized least squares model and included any significant autoregressive terms to control for correlation over time.²⁷ Changes in level were assessed using a binary variable that indicated the post-DTCA period, and changes in trend were assessed with a variable indicating the number of months that had passed since DTCA began. All analyses were conducted using the Autoreg procedure in SAS 9.1.³²

RESULTS

Total US DTCA spending for clopidogrel from 2001 to 2005 was more than \$350 million, or an average of \$70 million per year (**Figure 1**). National network news advertising occurred throughout the study period from the fourth quarter of 2001 onward (**Figure 2**).

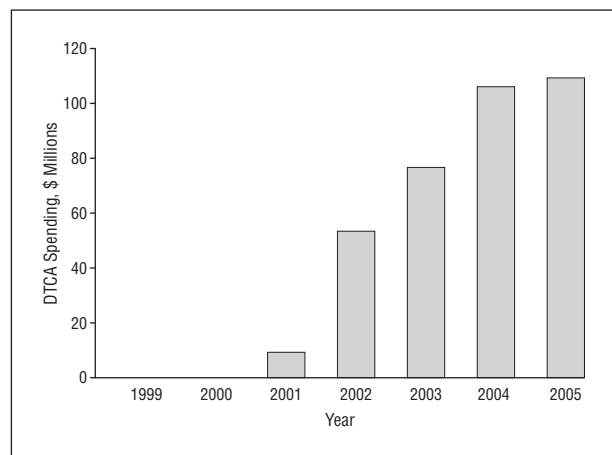


Figure 1. Estimated expenditure on direct-to-consumer advertising (DTCA) for clopidogrel from 1999 through 2005.

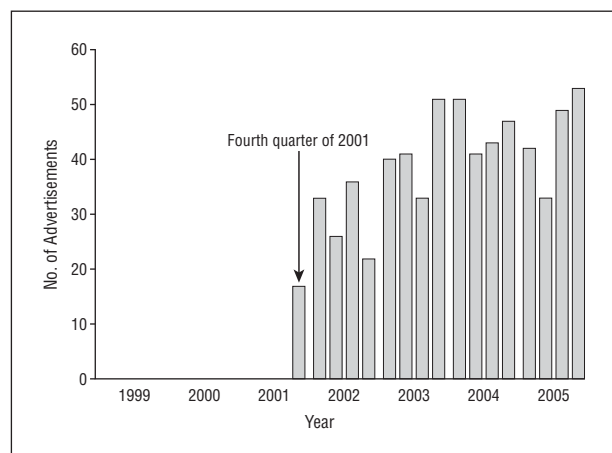


Figure 2. Quarterly number of US national network news direct-to-consumer advertising for clopidogrel from the Vanderbilt Television News Archive²⁹ from 1999 through 2005.

USE OF CLOPIDOGREL

As shown in **Figure 3**, clopidogrel use in the 27 Medicaid programs was increasing at a constant rate of 27.43 additional units per 1000 enrollees per quarter before the initiation of DTCA (95% confidence interval [CI], 23.38–31.49; $P < .001$). However, there was no clinically or statistically significant effect of DTCA on Medicaid rates of clopidogrel use in comparison to these preexisting trends. After the pre-DTCA trends were controlled for, the immediate change in the level of units dispensed per 1000 enrollees was -22.64 (95% CI, -56.84 to 11.56 ; $P = .18$). The estimated change in trend was a nonsignificant 3.86 (95% CI, -0.79 to 8.53 ; $P = .10$).

PHARMACY COSTS PER UNIT DISPENSED

In contrast, there was a significant increase in the level of pharmacy cost per unit per quarter after the start of DTCA (**Figure 4**). In the quarter before the initiation of DTCA, our model predicted a cost of \$3.40 per unit (95% CI, \$3.28–\$3.53). Immediately after DTCA initiation, we found a large, sudden, and statistically signifi-

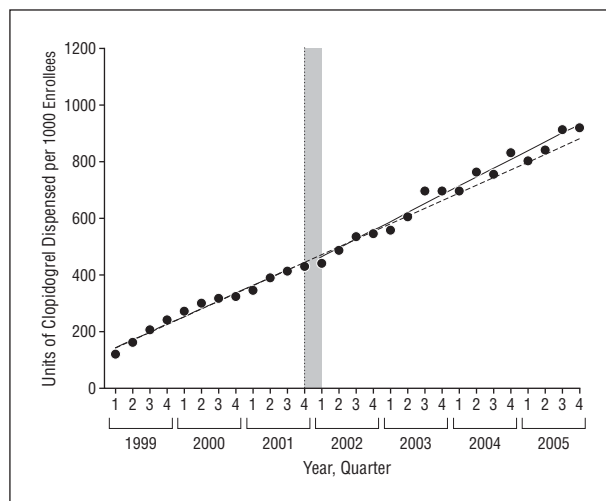


Figure 3. The number of clopidogrel units per 1000 enrollees per quarter in 27 Medicaid programs from 1999 through 2005. The vertical line and the gray bar indicate the start of network news advertising in the fourth quarter of 2001. The solid lines represent the fitted interrupted time series analysis, and the dashed line represents the expected use rate based on the pre-direct-to-consumer advertising (DTCA) trend. The analysis indicated no statistically significant change in either the level ($P = .18$) or the trend ($P = .10$) after DTCA initiation.

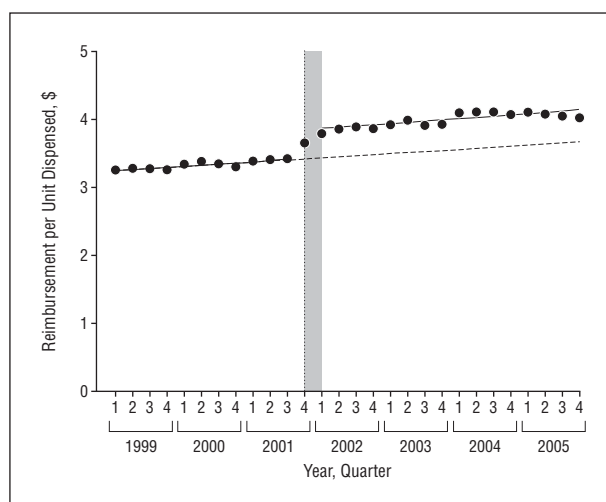


Figure 4. Pharmacy reimbursement per unit of clopidogrel per quarter in 27 Medicaid programs from 1999 through 2005. The vertical line and the gray bar indicate the start of network news advertising in the fourth quarter of 2001. The solid lines represent the fitted interrupted time series analysis, and the dashed line represents the expectation based on the pre-direct-to-consumer advertising (DTCA) trend. The analysis indicated a significant increase in level of \$0.40 per unit after DTCA initiation (95% confidence interval, \$0.31–\$0.49; $P < .001$). It indicated no statistically significant change in the existing trend ($P = .66$).

cant increase in the level of \$0.40 per unit (95% CI, \$0.31–\$0.49; $P < .001$). There was no significant change in the trend (estimate, \$0.0025; 95% CI, $-\$0.0094$ to $\$0.0145$; $P = .66$). Overall, these estimates translate into an immediate 12% increase in cost per unit dispensed after DTCA initiation.

TOTAL PHARMACY COSTS

This increase in the reimbursement per unit drove an increase in the total rate of pharmacy expenditure for clo-

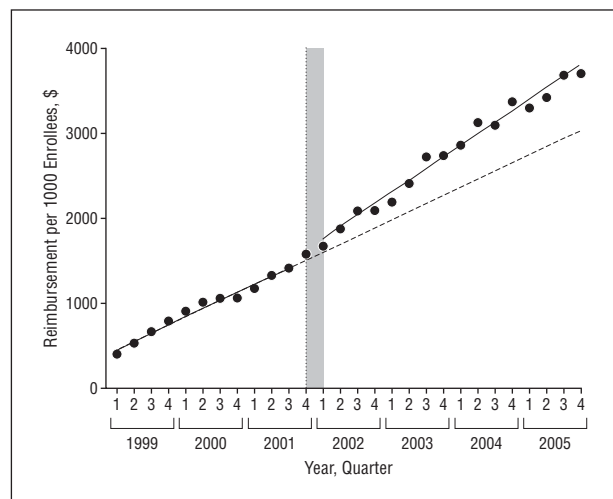


Figure 5. Total pharmacy reimbursement for clopidogrel per 1000 enrollees per quarter in 27 Medicaid programs from 1999 through 2005. The vertical line and the gray bar indicate the start of network news advertising in the fourth quarter of 2001. The solid lines represent the fitted interrupted time series analysis for the reimbursement rate, and the dashed line represents the expected rate had the pre-direct-to-consumer advertising (DTCA) trend continued. The analysis indicated a significant increase in trend of \$40.58 (95% confidence interval, \$22.61-\$58.56; $P < .001$) per quarter after DTCA initiation.

pidogrel (**Figure 5**). Before the initiation of DTCA, our model predicted costs were consistently rising at \$95.68 per 1000 enrollees per quarter (95% CI, \$80.35-\$111.00; $P < .001$). After the initiation of DTCA, the slope of this trend increased a further \$40.58 per 1000 enrollees per quarter (95% CI, \$22.61-\$58.56; $P < .001$). There was, however, no statistically significant immediate change in level of reimbursements associated with DTCA (estimate, \$58.90; 95% CI, -\$72.82 to \$190.62; $P = .36$). Overall, these estimates indicate a 25% increase in reimbursement by the end of 2005 beyond that which would be expected based on the existing pre-DTCA trend. Multiplying the increase in rate by the enrolled population in each quarter, this equates to an additional \$207 million in pharmacy reimbursement over the study period.

COMMENT

In the United States, the use of DTCA for pharmaceutical marketing has increased rapidly; for clopidogrel alone, it totaled \$350 million over 4 years. Somewhat unexpectedly, our results suggest that clopidogrel DTCA itself was not associated with an increase in the number of units of drug dispensed to Medicaid recipients. However, there was an almost simultaneous increase in pharmacy reimbursement associated with the start of DTCA owing to an increase in the cost per unit of clopidogrel. The net result confirmed our hypothesis: there was an overall increase in drug expenditures associated with the start of a DTCA campaign that amounted to an additional \$207 million dollars for 27 state Medicaid programs. These results may have implications for other heavily marketed drugs and for other public or private drug reimbursement programs.

Many claims in support or opposition to DTCA have relied on presumptions that it increases medication use.³³

For example, in supporting DTCA, Holmer³⁴ suggests that because a number of important conditions are underdiagnosed and undertreated (eg, diabetes, high cholesterol, depression, and hypertension), any strategy that informs consumers and prompts them to seek treatment will improve quality of care. Our analysis suggests that DTCA did not change existing trends in clopidogrel use among Medicaid patients. It is important to point out that Medicaid drug benefits typically have no or very low copayments, so any increase in price would not be passed on to enrollees but would be borne by the payer. This lack of effect on use is consistent with the results of our previous study, in which the long-term dispensing of 3 drugs (mometasone, etanercept, and tegaserod) was not influenced by DTCA.³³ Industry analysts have suggested that because DTCA increases sales, it allows companies to spread fixed overhead expenditure over a greater number of units, making drugs more affordable for the population as a whole; of course, this view would be true only if drug prices declined.³⁵ Our study of clopidogrel use in Medicaid provides no evidence that DTCA increases the number of units dispensed or reduces the cost per unit sold.

Nevertheless, our results are still consistent with an association between DTCA and higher Medicaid drug costs, although the mechanism is not through the commonly assumed increase in use. It is noteworthy that the start of a \$350 million advertising campaign coincided with an increase in the reimbursement per unit paid by Medicaid programs. We must assume that the extra reimbursement from Medicaid reflects an increase in the manufacturer's price for clopidogrel, because it is unlikely that there is any other plausible reason for such a sudden and large increase across 27 state programs.³⁶ However, as data on pricing are confidential, we cannot be sure. While offsetting the costs of DTCA may have been one of several potential motivations for the increase in per-unit cost of clopidogrel, other factors that might play a role in price setting include anticipating increased clopidogrel sales, concurrent changes in the sales of the manufacturers' other drugs, overall market conditions, and research and development costs for future products.³⁷

The major strength of our study is the use of a longitudinal time series analysis that controls for the existing level and trend of prescribing. Also, as our study focuses on a widely used and costly drug in a 6-year longitudinal analysis of more than 30 million Medicaid patients, our estimates of changes are very precise. We also acknowledge several shortcomings. First, our study focuses on only 1 drug, so it is unclear whether these results can be generalized. In particular, the release of important research studies and new indications during our study period may have altered how this particular drug responded to DTCA.³⁸ Furthermore, it is possible that DTCA prevented a plateau in prescribing rates that would have occurred otherwise. However, there is no indication of an impending plateau in our long baseline trend. Finally, the response to DTCA may differ in other drug classes in which several medications are heavily advertised, not just one, as is the case with clopidogrel.

Second, we could not examine the impact of DTCA on the appropriateness of clopidogrel prescribing given

that the main alternative antiplatelet agent (ie, aspirin) was available over the counter for the entire study period. This availability also precluded the use of aspirin as a control series. Third, many Medicaid recipients qualify for benefits by being of low income or disabled, so their response to clopidogrel DTCA may differ from higher-income or privately insured Americans. However, at least 1 example of previous research suggests that DTCA is more effective among individuals with low socioeconomic status.³⁹ Fourth, we have no measures of concurrent direct-to-physician marketing such as journal advertisements, samples, and office detailing. However, the DTCA campaign started several years after the product launch and likely start of physician marketing. Finally, our data on pharmacy reimbursement do not include any state-specific discounts related to other drugs or clopidogrel-specific rebates that Medicaid programs might receive from manufacturers. However, such agreements would only change the interpretation of our results in the unlikely circumstance that they were of similar magnitude to the reimbursement increases that we documented and broadly implemented at the same time that DTCA started. Of course, such discounts or rebates would not change our conclusions related to use.

Overall, our study has 2 implications. First, DTCA for clopidogrel had no statistically significant impact on Medicaid use levels. This finding contrasts with past studies that have concluded that DTCA increased use but that generally did not control for pre-DTCA trends.⁴⁰ However, other, stronger, interrupted time series studies have also demonstrated a lack of any substantial or sustained DTCA effect on use for 3 other heavily marketed drugs: mometasone, etanercept, and tegaserod.³³ Therefore, this study provides further evidence that DTCA is not always effective at increasing drug use. Second, DTCA can still be associated with higher drug costs if it is common practice to increase drug costs at the same time that campaigns are initiated. Consequently, payers and policy makers should appropriately still be concerned about DTCA increasing total drug costs for publicly funded reimbursement programs such as Medicaid and Medicare. Future longitudinal studies should examine other drugs and settings because many other countries are currently considering whether to permit DTCA.^{41,42}

Accepted for Publication: July 22, 2009.

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Author Contributions: Dr Law had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Law, Soumerai, and Majumdar. *Acquisition of data:* Law and Soumerai. *Analysis and interpretation of data:* Law, Soumerai, Adams, and Majumdar. *Drafting of the manuscript:* Law. *Critical revision of the manuscript for important intellectual content:* Soumerai, Adams, and Majumdar. *Statistical analysis:* Law and Adams. *Obtained funding:* Soumerai. *Administrative, technical, and material support:* Soumerai. *Study supervision:* Soumerai and Adams.

Financial Disclosure: Dr Soumerai reports no conflicts of interest, but he conducted a previous study of prior authorization of medications for schizophrenia that was supported by a public-private partnership program of the Agency for Healthcare Research and Quality (AHRQ), the Centers for Education and Research in Therapeutics (CERT), and the HMO Research Network CERT; Eli Lilly & Co; the Centers for Disease Control and Prevention; and the Harvard Pilgrim Health Care Foundation.

Funding/Support: This study was completed while Dr Law was supported by the Thomas O. Pyle Fellowship and the Fellowship in Pharmaceutical Policy at Harvard Medical School and a Social Sciences and Humanities Research Council of Canada Doctoral Fellowship. Drs Soumerai and Adams are investigators in the Health Maintenance Organization Research Network Centers for Education and Research on Therapeutics, which is supported by AHRQ grant U18HS010391 and the Harvard Pilgrim Health Care Foundation. Dr Majumdar receives salary support from the Alberta Heritage Foundation for Medical Research (Health Scholar).

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

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