

ONLINE FIRST

Variations in Pill Appearance of Antiepileptic Drugs and the Risk of Nonadherence

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Background: Generic prescription drugs are bioequivalent to brand-name versions but may not have consistent color or shape, which can cause confusion and lead to interruptions in medication use. We sought to determine whether switching among different-appearing antiepileptic drugs (AEDs) is associated with increased rates of medication nonpersistence, which can have serious medical, financial, and social consequences.

Methods: We designed a nested case-control study of commercially insured patients in the United States who initiated an AED. Cases were patients who became nonpersistent, defined as failure to fill a prescription within 5 days of the elapsed days supplied. Controls had no delay in refilling and were matched by sex, age, number of refills, and the presence of a seizure disorder diagnosis. We evaluated the 2 refills preceding nonpersistence and determined whether pill color and/or shape matched (“concordant”) or did not match (“discordant”). We compared the odds of discordance among cases and controls using multivariate conditional logistic regression, adjusting for baseline characteristics, and drug type. We repeated our analysis among patients with a seizure diagnosis.

Results: The AEDs dispensed had 37 colors and 4 shapes. A total of 11 472 patients with nonpersistence were linked to 50 050 controls. Color discordance preceded 136 cases (1.20%) but only 480 controls (0.97%) (adjusted odds ratio [OR], 1.27 [95% CI, 1.04-1.55]). Shape discordance preceded 18 cases (0.16%) and 54 controls (0.11%) (OR, 1.47 [95% CI, 0.85-2.54]). Within the seizure disorder diagnosis subgroup, the risk of nonpersistence after changes in pill color was also significantly elevated (OR, 1.53 [95% CI 1.07-2.18]).

Conclusions: Changes in pill color significantly increase the odds of nonpersistence; this may have important clinical implications. Our study supports a reconsideration of current regulatory policy that permits wide variation in the appearance of bioequivalent drugs.

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GENERIC PRESCRIPTION drugs become available after expiration of the brand-name product’s market exclusivity. In the United States, generic medicines account for over 70% of prescriptions dispensed, yet make up only 16% of spending.¹ Generic prescribing is expected to rise further as top-selling brand-name medications such as atorvastatin (Lipitor) and clopidogrel (Plavix) reach the end of their market exclusivity periods.² Appropriate use of generic drugs can reduce health care spending³ and promote adherence to medication regimens.⁴ Medication nonadherence is a common problem, as an estimated 50% to 75% of patients do not take their medications as prescribed,^{5,6} leading to increased morbidity, mortality, and potentially avoidable health care costs of

more than \$100 billion annually in the United States.⁷

Generic drugs approved by national regulatory authorities must be bioequivalent to the brand-name version, meaning they are comparable in dosage form, strength, route of administration, quality, intended use, and clinical efficacy.^{8,9} Despite such clinical bioequivalence, not all is equal: generic drugs do not have consistent color or shape compared with their brand-name versions or with each other. This occurs because the US Food and Drug Administration (FDA) does not require similarity in appearance¹⁰ and because pharmaceutical companies may claim legal protection of physical attributes of their pills—such as color, shape, size, texture, aroma, and flavor—under a subset of trademark law called “trade dress.”¹¹⁻¹³ Some drugs may therefore vary widely in

their appearance.¹⁴ A patient taking 5 medicines, each produced by 5 generic manufacturers, theoretically faces over 3000 possible arrays of pill appearances for what are, chemically and clinically speaking, the same drugs.¹⁵

Differences in the appearance of otherwise interchangeable drugs may have important effects on patient care. Changes between generic products with different physical characteristics may cause confusion and result in reduced adherence^{16,17} or prescription error.^{18,19} Case reports suggest this may be more likely among patients with complicated medication regimens and/or limited health literacy.²⁰ However, we could find no empirical studies of the consequences of changes in pill appearance in a population-based analysis.

Therefore, we sought to determine whether switching among different-appearing pills is associated with changes in medication adherence in a national cohort of commercially insured patients. We tested this question among users of antiepileptic drugs (AEDs). Epilepsy is a common disease, affecting about 1% to 2% of people, and AEDs are also used off-label for psychiatric disease, chronic pain, and other conditions.²¹ In patients with epilepsy, even short interruptions in medication supply can lead to loss of seizure control²² and have substantial medical, financial, and social consequences.²³ In recent years, many widely used brand-name AEDs have lost market exclusivity,²⁴ so we used a case-control study design to evaluate whether there is a link between changes in the shape and color of the dispensed pills and nonpersistence to AEDs.

METHODS

STUDY DESIGN

We conducted a nested case-control study of patients initiating an AED and compared the odds that patients who became nonpersistent with their medication had filled prescriptions for pills that differed in size and/or color from the prior prescription. While adherence and persistence are closely related concepts, this study technically measured persistence, the duration of time from initiation to discontinuation of therapy.²⁵ The study was approved by the institutional review board at Brigham and Women's Hospital, Boston, Massachusetts.

DATA SOURCES

Medical and pharmacy data were collected from the HealthCore Integrated Research Database (HIRD). The HIRD contains longitudinal health care claims data representing all filled prescriptions and clinical encounters from commercial Blue Cross/Blue Shield health plans in the southeastern, mid-Atlantic, central, and western regions of the United States. Medical diagnoses are coded according to the *International Classification of Diseases, Ninth Revision (ICD-9)*. Drug prescriptions were identified by National Drug Code (NDC) number. Data were available from January 2004 through December 2006 for 14 US states (Delaware, Georgia, California, Virginia, New York, Nevada, Indiana, Kentucky, Missouri, Ohio, Wisconsin, Connecticut, Maine, New Hampshire), with 3 states (Delaware, Georgia, California) having data dating back to July 2001.

Prescriptions claims data were linked by NDC number to the First DataBank National Drug Data File, which contains descriptive drug information, including the formulation type (cap-

sule, tablet, oral suspension, etc), dose strength, and precise color and shape.

ANTIEPILEPTIC DRUGS

We included patients filling prescriptions for drugs that (1) had been approved specifically for use in treating seizures, (2) were available in pill form, and (3) had at least 1 brand-name and 1 generic form available on the US market during the study period (2001-2006). The 8 AEDs meeting these criteria were carbamazepine, carbamazepine extended-release, ethosuximide, lamotrigine, phenytoin sodium, valproic acid, gabapentin, and zonisamide (all doses). We excluded gabapentin because its use during this time period was nearly exclusively for off-label indications outside of epilepsy.²⁶ We merged the remaining drugs to obtain class-level estimates of the effect of color and shape discordance.

IDENTIFICATION OF CASES AND CONTROLS

We identified all patients who filled a first prescription after January 1, 2002, for 1 of the 7 AEDs in our study, after a period of 6 months of continuous health plan enrollment during which they had not filled a prescription for any anticonvulsant, and defined this first dispensing as the index date. If a patient was prescribed more than 1 eligible drug, we treated each record as a separate entry. Among these patients, we defined the range of pill color patterns and shape types using the First DataBank National Drug Data File.

Cases were patients who had incomplete persistence to their index AED, defined as failure to fill a new prescription for the drug within 5 days of the elapsed days supplied. To identify cases, we first created a supply diary of prescription drug filling after each patient's index date and then calculated the accumulated days' supply. If a new dispensing occurred before the prior days' supply ran out, we carried the extra days over. The date on which a patient became nonpersistent was their "outcome date." Since we then looked at color and shape discordance in the prior dispensing (see the subsection titled "Pill Color and Shape"), cases were required to have a minimum of 3 dispensings (that is, the index date defining initial fill and 2 refills) of the same drug, dose, and route. To limit duplicate contributions to the pool of cases, we selected only the patient's first episode of nonpersistence for a given drug. For patients taking multiple AEDs, we conservatively allowed them to become a case only at the first observed episode of nonpersistence and did not allow them to be a case for subsequent episodes for other drugs.

Controls were identified using the same methodology but had no gap in therapy. Controls were matched to cases based on the specific AED used, the number of dispensings, sex, age (within 5 years), and the presence of a seizure diagnosis (see the subsection titled "Covariates"). We permitted controls to be matched up to more than 1 case and selected a maximum of 5 controls per case. Cases could be controls for other patients prior to an episode of nonpersistence.

PILL COLOR AND SHAPE

For each case and control, we evaluated the 2 refills prior to the outcome date. We excluded cases and controls in whom the 2 refills prior to the final date were for different doses of the drug, or if shape or color data were missing or unknown. We then determined whether the 2 prior refills were matching ("concordant") or not matching ("discordant") in terms of color and shape. We noted the rates of color discordance and shape discordance separately for all cases and controls.

Table 1. Shape Variation Among Antiepileptic Prescriptions in Sample

Shape Type	Type of Drug, No. (%)						
	Carbamazepine	Carbamazepine-XR	Lamotrigine	Zonisamide	Ethosuximide	Valproic Acid	Phenytoin Sodium
Round or circular	47 450 (78.3)	31 227 (56.6)	0	0	0	0	0
Oval or elliptical	0	0	0	0	0	365 (32.4)	0
Oblong	12 753 (21.1)	14 736 (26.7)	4 (0)	5438 (97)	38 668 (99.5)	760 (67.6)	12 3814 (100)
Shield	0	0	263 906 (99.9)	0	0	0	0
Unknown	365 (0.6)	9217 (16.7)	134 (0.1)	168 (3)	181 (0.5)	0	2 (0)
Total	60 568 (100)	55 180 (100)	264 044 (100)	5606 (100)	38 849 (100)	1125 (100)	123 816 (100)

COVARIATES

We defined demographic characteristics of the cases and controls, including age at index date and sex. We also identified health services utilization for cases and controls during the 6 months prior to the index date, including the number of non-AED prescriptions, number of outpatient physician encounters, and number of emergency department visits or inpatient hospitalizations. Finally, we collected data on diagnoses listed during the 6 months prior to the index date, including seizure disorder (ICD-9 codes 345 and 780.3), pain syndrome (ICD-9 codes 338, 346, 350, 354, 355, 356, 357, 729.1, 353), episodic mood disorder (ICD-9 code 296), or other psychiatric disorders (ICD-9 code 295).

STATISTICAL ANALYSIS

We generated descriptive statistics and performed matched case-control analyses using bivariate and multivariate conditional logistic regression. The dependent variable in all regression analyses was a binary variable distinguishing cases from controls. After excluding the matching variables, we included all remaining baseline covariates in the adjusted model along with a variable to account for differences across drug type. We then repeated the analysis in the subgroup of patients who had a seizure diagnosis in the 6 months prior to the index date and included the same covariates in the adjusted model.

To test the sensitivity of our findings, we changed our definition of nonpersistence to be more (3 days) and less (10 days) restrictive. All analyses were conducted using the SAS statistical package (version 9.2; SAS Institute).

RESULTS

We identified 62 928 individuals who initiated an AED during the study period, of whom 60 741 had at least 6 months of continuous enrollment prior to their index date. This group made up the pool of potential cases and controls for our study.

PILL SHAPE AND COLOR VARIATIONS

Among cases and controls, antiepileptic drugs displayed 37 different color arrangements and 4 different shape types (**Table 1** and **Table 2**). Within the study drugs, valproic acid pills displayed the least color variation—100% were orange—while ethosuximide displayed the most variation, with 19 different color possibilities, including yellow (84 prescriptions [0.2% of ethosuximide prescriptions]), blue-violet (3031 [7.8%]), and white and red (29 053 [74.8%]), which was the most common shade.

Differences in pill shape variation were less common, with 4 drugs (lamotrigine, zonisamide, ethosuximide, and phenytoin) being produced nearly exclusively in a single shape, and the remainder being split mostly between 2 shapes. For example, carbamazepine extended-release pills came in 8 different colors (black and blue-green, blue and yellow, blue and green, brown, gray and blue-green, pink, yellow, yellow and blue-green), but only 2 different shapes: round or circular (31 227 prescriptions [56.6% of carbamazepine extended-release prescriptions]) and oblong (14 736 [26.7%]).

CHARACTERISTICS OF CASES AND CONTROLS

We identified 11 472 patients with episodes of AED non-persistence who were matched to 50 050 control patients. **Table 3** shows that cases and controls were similar in terms of demographics. About one-fifth of cases and controls were linked to a diagnosis of seizure disorder. Episodic mood disorder and pain disorders were slightly more common among cases than among controls. Both cases and controls averaged about 9 outpatient physician encounters in the past 6 months and about 30 filled prescriptions during that time.

MULTIVARIATE ANALYSIS

Overall, color and shape discordance occurred infrequently but was more common preceding cases of antiepileptic drug nonpersistence. In our full sample, color discordance occurred in 136 cases (1.20%), while shape discordance occurred in 18 cases (0.16%). Discordance rates were similar among the subset of antiepileptic drug use cases linked to diagnoses of seizure disorders (1.74% and 0.16%, respectively).

Cases were significantly more likely to have had preceding color discordance than controls (**Table 4**). The odds of color discordance occurring immediately before a filling gap was 27% greater than in controls for whom no interruption in therapy was observed (adjusted odds ratio [OR], 1.27 [95% CI, 1.04-1.55]). Among patients with a seizure disorder, the adjusted odds of a color discordance occurring immediately before a prescription gap was 53% greater than in controls in whom no break was observed (adjusted OR, 1.53 [95% CI, 1.07-2.18]). The odds of a shape discordance occurring was also greater in cases than in controls, but the difference was not statistically significant in either the full sample (adjusted

Table 2. Color Variation Among Antiepileptic Prescriptions in Sample

Antiepileptic Drug	Color and Prevalence, No. (%) ^a					
	Most Common	Second Most Common	Third Most Common	Fourth Most Common	Fifth Most Common	Others
Carbamazepine	White, 47 477 (78.4)	Pink, 12 753 (21.1)	NA	NA	NA	NA
Carbamazepine-XR	Pink, 15 356 (27.8)	Black and blue-green, 10 747 (19.5)	Brown, 10 141 (18.4)	Gray and blue-green, 6767 (12.3)	Yellow, 5730 (10.4)	Blue-yellow, 1457 (2.6); yellow and blue-green, 159 (0.3); blue-green, 56 (0.1)
Lamotrigine	Peach, 127 824 (48.4)	Blue, 57 118 (21.6)	White, 52 172 (19.8)	Cream, 26 618 (10.1)	Multicolor, 178 (0.1)	NA
Zonisamide	Off-white, 3384 (60.4)	White, 1540 (27.5)	Yellow, 530 (9.5)	Orange, 79 (1.4)	Beige, 42 (0.7)	NA
Valproic acid	Orange, 1125 (100)	NA	NA	NA	NA	NA
Phenytoin sodium	White and violet, 62 935 (50.8)	Clear or colorless, 55 247 (44.6)	Blue, 5482 (4.4)	Natural, 116 (0.1)	White and lavender, 24 (0)	Orange, 10 (0)
Ethosuximide	White and red, 29 053 (74.8)	Blue/violet, 3031 (7.8)	White and gray, 1600 (4.1)	White, 1421 (3.7)	White and green, 669 (1.7)	Red and gray, 602 (1.5); white and orange, 596 (1.5); white and peach, 505 (1.3); violet and lavender, 303 (0.8); white and violet, 289 (0.7); orange, 287 (0.7); gray/gray, 101 (0.3); yellow, 84 (0.2); white and blue, 65 (0.2); white and yellow, 52 (0.1); red-orange, 11 (0); iron gray, 6 (0); pink and peach, 4 (0); gray and red-orange, 1 (0)

Abbreviations NA, not applicable; XR, extended release.

^aPercentages may not sum to 100% due to colors listed as "unknown" in the database.

Table 3. Characteristics of Patients Serving as Cases and Controls

Characteristic	Cases (n = 11 472)	Controls (n = 50 050)
Age, mean (SD), y	42.9 (15.3)	42.9 (14.7)
Female sex, No. (%)	6854 (59.8)	29 843 (59.6)
Total No. of AED refills, mean (SD)	6.6 (5.5)	6.4 (5.0) ^a
Diagnoses, No. (%)		
Seizure disorder	2579 (22.5)	11 738 (22.8)
Episodic mood disorder	3409 (29.7)	13 199 (28.0) ^a
Pain disorder	1602 (14.0)	6265 (12.5) ^a
Other psychiatric disorder	122 (1.1)	476 (1.0)
Non-AED prescriptions in the past 6 mo, mean (SD)	29.5 (29.8)	29.4 (29.4)
Inpatient/emergency visits in past 6 mo, mean (SD)	0.75 (1.6)	0.63 (1.3) ^a
Outpatient physician encounters in past 6 mo, mean (SD)	9.3 (10.6)	9.2 (11.0)

Abbreviation: AED, antiepileptic drug.

^aStatistically significant difference at $P < .001$.

OR, 1.47 [95% CI, 0.85-2.54]) or patients linked to a diagnosis of a seizure disorder (adjusted OR, 3.15 [95% CI, 0.82-12.1]) (**Figure**). In sensitivity analysis, we found that neither shortening the break in elapsed days supplied from 5 to 3 days nor lengthening it to 10 days substantially changed the ORs or the statistical significance of the results.

COMMENT

Although the influence of pill appearance on patient behavior has long been a source of concern for clinicians, this is the first empirical analysis, to our knowledge, linking pill characteristics to patients' medication adherence. Bioequivalent AEDs can have a variety of shapes and colors, and we found that patients who experience changes in pill color in particular have an increased risk of interruptions in medication use.

Several potential explanations may account for these findings. First, drugs are commonly removed from their bottles to assist in organization, such as when patients or caregivers sort their medications into pill planners²⁷ or pharmacists provide blister packs to patients.²⁸ Visual cues thus become paramount to identification of pills, and changes in appearance may be jarring or confusing, leading patients to delay pill-taking while seeking validation from a physician, pharmacist, or other health care provider. In this sample of medications, changes to pill color may be more noticeable than changes in shapes, which were commonly of the more subtle round or circular to oblong variety. Another alternative is that the smaller number of shape changes did not provide enough power to find a statistically significant effect.

The placebo effect, a vital though often ignored part of therapeutic intervention,²⁹ may also contribute to our results. A pill's physical attributes have been linked to expectations of efficacy of both placebos and pharmacologically active prescription drugs.³⁰ Thus, changes in pill

Table 4. Association Between Nonadherence and Color and Shape Discordance in Antiepileptic Drugs

Sample or Subset	No. (%)		OR (95% CI)	
	Discordance Among Cases	Discordance Among Controls	Unadjusted	Adjusted
Main sample				
Color discordance	136 (1.20)	480 (0.97)	1.29 (1.06-1.57)	1.27 (1.04-1.55)
Shape discordance	18 (0.16)	54 (0.11)	1.52 (0.88-2.62)	1.47 (0.85-2.54)
Subset with seizure diagnoses				
Color discordance	45 (1.74)	133 (1.16)	1.54 (1.08-2.20)	1.53 (1.07-2.18)
Shape discordance	4 (0.16)	6 (0.05)	3.22 (0.83-12.4)	3.15 (0.82-12.1)

Abbreviation: OR, odds ratio.

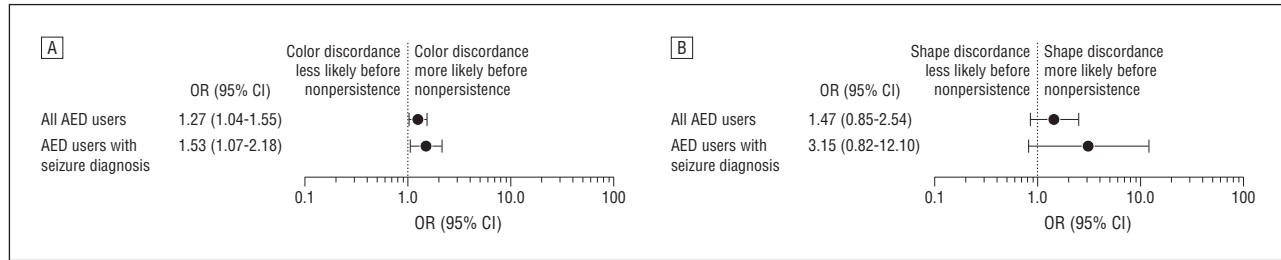


Figure. Comparison of odds ratios (ORs) or color (A) and shape (B) discordance related to antiepileptic drug (AED) nonadherence.

appearance may not only deprive patients of these expectations of efficacy, but potentially even have the opposite effect—a belief that the newly substituted pill will be less efficacious (the so-called nocebo effect).³¹ Nonpersistence may result.

Controversies over pill substitution are particularly salient among AEDs. In response to case reports³² and observational studies³³ claiming that bioequivalent generic AEDs may not have the same clinical effects as their brand-name counterparts, some physician professional organizations³⁴ and patient advocates³⁵ have opposed the routine interchange of bioequivalent AEDs. Several US states have also entertained or passed legislation to limit substitution of generic AEDs³⁶⁻³⁸ to “protect patients from breakthrough seizures.”³⁹ However, other well-controlled studies have refuted these concerns,⁴⁰ supporting the safety of substituting bioequivalent brand-name and generic AEDs.⁴¹ Our study suggests that nonpersistence related to changes in color may be one unmeasured factor contributing to negative reports about bioequivalent generic AEDs. Changes in pill appearance may create a self-fulfilling prophecy in which therapeutically bioequivalent regimens actually become less clinically effective owing to induced nonpersistence.

If replicated in other settings, these findings could have additional important implications. In caring for patients who are nonadherent, physicians might consider the contribution of varying pill color. In the near term, as more widely used brand-name drugs face generic competition, physicians should warn patients about the possibility that pill color might change, and pharmacists might take greater care to alert patients when changes in suppliers lead to new pill characteristics. At pharmacies, the ability to alert consumers when pill features have changed may require adaptations to information technology systems. Educating consumers about the safety and effi-

cacy of approved generic drugs—no matter what physical attributes the drug possesses—may also help mitigate the effect we observed in this study.

Our study also supports a reconsideration of current regulatory policy that permits wide variation in the appearance of bioequivalent drugs. In the United States, the FDA has recently started rejecting generic drugs that are larger in size than their brand-name counterpart, citing safety and efficacy concerns, such as increased risk of choking and patient dissatisfaction.⁴² Based on our results, the FDA would be justified in taking a similar posture about new generic drugs that differ in color, although a blanket requirement for equivalence in pill appearance may require formal rulemaking. One pertinent precedent in this area occurred in the United Kingdom, which systematized color coding of metered-dose inhalers for asthma after noting that users frequently confused bronchodilators for steroid inhalers.⁴³ As a result, the National Health Service mandated that all bronchodilators appear blue, while all steroids appear brown, orange, or burgundy.¹³ At a minimum, our results should clarify that manufacturers cannot protect their drugs’ physical characteristics through the principle of trade dress. Such legal protection requires that relevant attribute be nonfunctional, and our study demonstrates the functional importance of pill appearance in promoting therapeutic equivalence among AEDs.

There are several limitations to this study. First, while pharmacy claims have been used to track adherence in numerous studies,^{44,45} a filled prescription does not prove that the patient actually took the medication. Similarly, what we observed as nonpersistence may have been physician-directed changes in medication dosing frequency. Second, the absolute magnitude of the effect observed in our study was small, so changing appearance may have a small overall effect on medication adher-

ence. However, previous research shows that patients with epilepsy who are nonadherent to their treatment have increased risk of seizure-related emergency department visits and even mortality.⁴⁶ Since changes in medication use for epilepsy and other important conditions can have substantial clinical impact, we should seek simple approaches to reduce these adverse outcomes, like maintaining consistency in pill color. We also could not examine other changes within the pills, such as changes in the coating or filler, that might accompany changes in color and affect the way that patients with epilepsy perceive their medication. Such changes have anecdotally increased the risk of nonadherence in patients with epilepsy,⁴⁷ but not conclusively demonstrated to reflect legitimate differences in the drugs.⁴⁸ We limited our definition of nonpersistence to 5 days, although the results were consistent at 10 days, and even such a short break in therapy can be dangerous, particularly for patients with seizure disorders. Finally, our focus on AEDs limits generalizability of these results, since patients on AEDs and their treating physicians may be particularly attentive to their pills' appearances.

Despite these limitations, our study indicates that changes in pill color are associated with a significant increase in the risk of nonadherence. Promoting medication adherence is a difficult task, and it has been only partially addressed through strategies such as enhanced prescribing of generic drugs⁴⁹ and reducing drug copayments.⁵⁰ Taking steps to permit (or even require) similarity in pill appearance among bioequivalent brand-name and generic drugs may offer another way to achieve better patient adherence to essential medication regimens.

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Author Contributions: Dr Kesselheim had full access to all of 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:* Kesselheim, Misono, Shrank, Greene, Avorn, and Choudhry. *Acquisition of data:* Kesselheim, Misono, Shrank, and Doherty. *Analysis and interpretation of data:* Kesselheim, Misono, Shrank, Greene, Doherty, and Choudhry. *Drafting of the manuscript:* Kesselheim, Misono, and Greene. *Critical revision of the manuscript for important intellectual content:* Kesselheim, Misono, Shrank, Greene, Doherty, Avorn, and Choudhry. *Statistical analysis:* Shrank and Doherty. *Administrative, technical, and material support:* Misono, Shrank, and Doherty. *Study supervision:* Shrank, Avorn, and Choudhry.

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