Warnings Without Guidance

Patient Responses to an FDA Warning About Ezetimibe

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Background: In January 2008, the Food and Drug Administration (FDA) communicated concerns about the efficacy of ezetimibe, but did not provide clear clinical guidance, and substantial media attention ensued. We investigated the proportion of patients who discontinued therapy and switched to a clinically appropriate alternative after the FDA communication.

Methods: Using claims data from a national pharmacy benefits manager, we created a rolling cohort of new users of ezetimibe between January 2006 and August 2008 and created a supply diary for each patient in the year after cohort entry. A patient was identified as nonpersistent if a gap of 90 days was seen in the diary. Using segmented linear regression, we compared rates of nonpersistence before and after the FDA communication and assessed patient-level characteristics associated with discontinuation. Among nonpersistent patients, we determined whether a patient made a clinically appropriate switch in the subsequent 90 days by adding a new cholesterol-lowering medication or by increasing the dose of an existing one. We used a weighted *t* test to compare the rates of appropriate switching before and after the communication.

Results: Among 867,027 new ezetimibe users, 407,006 (46.9%) were nonpersistent in the first year. After the FDA communication, the monthly level of ezetimibe nonpersistence increased by 5.7 percentage points ($P < 0.0001$). Younger patients, those who lived in low-income zip codes, and female patients were less likely to discontinue therapy ($P < 0.0001$ for all). Among nonpersistent patients, rates of clinically appropriate switching increased from 10.8% before to 16.5% after the FDA warning ($P = 0.004$).

Conclusions: A substantial increase in ezetimibe nonpersistence rates was seen after an FDA communication regarding its efficacy and following associated media attention, and a small proportion of patients made a clinically appropriate switch after discontinuation. Further consideration is needed to deliver messages that promote appropriate use of chronic therapy rather than simply reduce use.

Key Words: medication, FDA warning, adherence

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BACKGROUND

On January 25, 2008, the Food and Drug Administration (FDA) issued an "early communication about an ongoing review" regarding the cholesterol-lowering medication, ezetimibe, after results from the ENHANCE trial indicated that adding ezetimibe to simvastatin led to a nonsignificant increase in coronary artery intimal wall thickness.[1] The communication stated that the "FDA is not advising health care professionals to discontinue prescribing these products." Rather, the FDA highlighted the lack of efficacy seen in the primary clinical outcome in the ENHANCE trial, raising important questions about the medication's effectiveness, and indicated that continued review was underway. Substantial media attention followed.

A number of studies have demonstrated that FDA warnings about the safety or efficacy of drug products lead to reduced rates of physician prescribing and patient use of medication.[2–7] For medications that pose greater risk than benefit, these reductions, when coupled with appropriate switching to a safer or more effective therapeutic option, can lead to improved patient care. Little is known, however, about how patients and physicians respond to more vague communications without recommendations on how to alter clinical decision making. Moreover, when patients discontinue therapy with a medication in response to any type

of communication, we know little about the rates at which patients find an appropriate substitute—a different medication to treat the same condition—or discontinue therapy altogether and fail to appropriately manage the underlying illness. The clinical implications for patients with chronic disease could be of great consequence.

Using pharmacy claims from a large national pharmacy benefits manager, we evaluated the use of ezetimibe and other cholesterol-lowering medications before and after the FDA communication was issued, exploring the rates of discontinuation of ezetimibe before and after the warning. Among those who discontinued, we evaluated whether patients switched to an appropriate clinical alternative. We aimed to better understand the patterns of medication use after the FDA communication and associated media attention, as well as the patient-level correlates of this behavior. Such information is essential to provide guidance about how to optimally deliver warning messages that will improve disease management.

METHODS

Cohort Construction

Using complete pharmacy claims from CVS Caremark, we identified all patients who received prescription drug coverage from Caremark, a national pharmacy benefits manager, and who filled a new prescription for ezetimibe (either as Zetia or as the ezetimibe-simvastatin combination, Vytorin) between January 1, 2006 and July 31, 2008. A new prescription was defined as a fill for ezetimibe by a patient who had no prior fills for the medication in the previous 6 months.[8] The date of the first fill of ezetimibe was defined as the index date. We excluded patients who were less than 18 years old.

For each patient included, we used pharmacy claims to identify his or her age, sex, geographic region, and type of pharmacy benefit coverage (eg, employer-sponsored, Medicare, or Medicaid) at the time of the index date. We identified the zip code of residence of each patient in the cohort and linked it to the median income of the area falling under that zip code using publicly available data from the 2000 US census, and identified the copayment of each index prescription. We calculated the total number of unique medications from all drug classes filled in the 3 months before the index data as a proxy for patient comorbidity.[9] We also identified the use of all other cholesterol-lowering medications in the 6 months before and 12 months after the ezetimibe index date.

We then created a rolling cohort of ezetimibe users. We allowed patients to enter the study at any time during our study period upon filling their index prescription for ezetimibe. Each patient remained in the study cohort for 365 days after their index date or until they were censored on October 31, 2008, whichever came first. We used a rolling cohort to allow patients to join over time and standardized the length of participation on the cohort to reduce bias related to the time-varying nature of medication adherence behavior. For each patient, we created a supply diary of ezetimibe. The supply diary for each patient was generated by stringing together consecutive dispensings of ezetimibe based on dispensing dates and the reported days' supply.

Outcome Assessment

Our primary outcome was ezetimibe discontinuation. We defined discontinuation at the patient level as the failure to refill an ezetimibe prescription within the 90 days after the supply diary has indicated that the supply had been exhausted. If a patient did not have a 90-day gap in therapy in the first 9 months of treatment of ezetimibe, they were considered persistent, as each patient was censored after 1 year. The nonpersistent date was defined as the date that the previous prescription was filled. We calculated monthly nonpersistence rates for the entire cohort. This rate was calculated as the number of patients in the cohort who became nonpersistent in any calendar month divided by the total number of patients in the cohort during that month.

Among those patients who were identified as nonpersistent, we assessed whether they made a clinically appropriate substitution in the 90 days subsequent to ezetimibe discontinuation. Two types of changes were defined as a clinically appropriate substitution: (1) addition of a new cholesterol-lowering medication (which could include statins or any other prescription treatment indicated to reduce cholesterol); or (2) increasing the dose of an existing cholesterol medication (one that the patient had filled any time during the study period before becoming nonpersistent to ezetimibe). We conducted sensitivity analyses stratifying patients by whether they used ezetimibe and Vytorin. We also conducted sensitivity analyses evaluating the rates of clinically appropriate switching using a 180-day follow-up period to determine switching behavior. Rates of clinically appropriate switching were qualitatively similar in those taking ezetimibe and those taking Vytorin, and rates of switching increased only marginally when a 180-day follow-up period was used. Only the base case has been presented here.

Analytic Approach

The analytic approach was developed to evaluate changes in the rates of discontinuation and appropriate substitution before and after the FDA warnings and associated media attention. We used descriptive statistics to present the characteristics of new users of ezetimibe in our cohort. We calculated and graphically presented monthly, aggregated discontinuation rates of ezetimibe. Graphical displays began 9 months after the cohort start date in order to reduce the irregularities caused by time-varying cohort effects. Among patients who discontinued ezetimibe each month, we calculated the proportion that made a clinically appropriate substitution and the proportion that did not, and we have graphically presented those monthly proportions.

To evaluate cohort trends in nonpersistence, we used a segmented linear autoregressive model that assumed normally distributed errors correlated at a lag of 1 month to estimate separate linear trends of monthly rates of ezetimibe discontinuation before and after the FDA warning had been issued. The model included a constant term and linear terms to estimate the trends in discontinuation rates during 3 distinct time periods: (1) before the communication (January

2006–December 2007); (2) during the transition period, at which time the FDA communication was issued (December 2007–January 2008); and (3) after the communication (January 2008–July 2008).[10] Among nonpersistent patients, we performed a weighted *t* test to compare the average rate of clinically appropriate substitution across the months before and after the FDA warning, in which the weights corresponded to the number of patients in the denominator of the rate each month (the number of patients who discontinued ezetimibe).

To assess patient-level characteristics associated with nonpersistence, we fit a segmented Poisson regression model to estimate trends in the rates of discontinuation before and after the FDA communication, adjusting for patient characteristics. This model included indicators for the calendar months January–December to adjust for seasonality in nonadherence. It also included indicator terms for the number of months on treatment for each patient (1-10) to adjust for patterns in nonpersistence associated with time on treatment. Discontinuation over the course of the study was modeled in 3 linear segments as above. To evaluate how reactions to the FDA communication and media attention differed among patients with varying demographic characteristics, we included interactions between patients' age group, sex, and income quintile and the change in nonpersistence rates during the transition period. The model also adjusted for the region of residence and the number of unique medications for each patient. This research was approved by IRBs at Harvard University and Brigham and Women's Hospital. All analyses were conducted using SAS 9.2 (Cary, NC).

RESULTS

We identified 867,027 new ezetimibe users meeting our inclusion criteria during the study period. Sample characteristics are presented in Table 1. Over 88% of patients were older than 50, 53% were female, and 20% filled prescriptions for 9 or more unique medications in the 3 months before the index date. Of the patients in our cohort, 407,006 (46.9%) were nonpersistent in the subsequent year. Of those, 12.8% restarted ezetimibe during the remainder of the year.

Aggregate monthly rates of ezetimibe nonpersistence are presented in Figure 1. A notable increase was seen in January 2008. Results from segmented linear regression analyses are presented in Table 2. During the transition period, the monthly level of nonpersistence to ezetimibe increased by 5.7 (95% confidence interval, 4.7–6.8) percentage points ($P < 0.0001$). After an immediate increase in nonpersistence rates after the FDA warning, we found a negative slope in the ezetimibe nonpersistence rates, indicating that the discontinuation rate shifted toward prewarning levels in the 9 months after the warning had been issued (Fig. 2).

Rates of clinically appropriate switching after ezetimibe discontinuation were low before the FDA warning and increased modestly after the warning was issued. A mean of 10.8% of patients who stopped ezetimibe made a clinically appropriate switch in the period before the FDA warning, and a mean of 16.5% made a clinically appropriate switch in the period after the warning, resulting in a statistically significant difference of 5.7% in switching ($P = 0.004$).

TABLE 1. Sample of Incident Ezetimibe Users (n = 867,027)

Characteristics	Percent (Frequency)
Age group	
18–34	0.9 (7.549)
35–49	10.4 (89.450)
50–64	40.0 (345.760)
65–107	48.7 (420.318)
Sex	
Female	52.8 (454.550)
Male	47.2 (406.765)
Income category	
$0–$33,584	21.1 (170.073)
$33,585–$40,597	20.1 (162.695)
$40,598–$49,636	19.9 (160.644)
$49,637–$61,737	19.6 (158.188)
$61,738–$200,001	19.3 (155.903)
Copayment	
$0	3.8 (33.065)
$0.01–$10.00	21.1 (182.989)
$10.01–$20.00	37.1 (321.797)
$20.01–$30.00	18.8 (163.287)
$30.01–$40.00	5.8 (49.971)
$40.01–$50.00	3.2 (27.808)
$50.01 and above	10.2 (88.101)
Unique number of medications	
0–2	18.3 (158.155)
3–5	37.2 (322.176)
6–8	24.6 (213.373)
9+	20.0 (173.012)
Insurance type	
Employer health plan	50.8 (440.694)
Other	4.6 (40.015)
Private insurance	20.7 (179.738)
Medicare	22.3 (193.528)
Medicaid	1.5 (13.052)
Region	
Northeast	28.3 (245.257)
Midwest	20.3 (176.189)
South	35.4 (307.048)
West	10.1 (87.392)
Other	5.9 (51.141)

In our model that adjusts for patient-level characteristics, the trends in nonpersistence over the course of the study were similar to those presented above (Table 3). The nonpersistence rates in the months before the FDA communication were not significantly different among demographic groups. However, several patient characteristics were associated with discontinuation rates after the FDA warning had been issued. Patients who resided in lower-income zip codes were less likely to discontinue therapy after an FDA warning had been issued. Comparing the months immediately before and after the warning, patients living in the lowest median income quintile had a 12.9% lower rate ratio of discontinuation compared with patients living in the highest income zip code ($P < 0.0001$), even after adjusting for type of insurance coverage. Female patients had 6.9% lower rate ratio of discontinuation compared with male patients ($P < 0.0001$). Younger patients were less likely to discontinue therapy after a warning compared with older patients; patients 18–34, 35–49, and 50–64 had 32.4%,

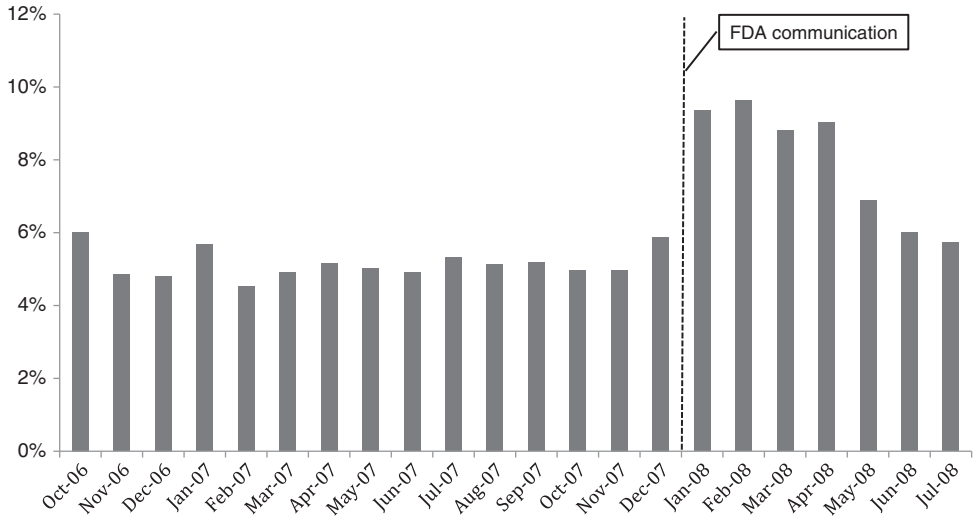

FIGURE 1. Monthly rates of nonpersistence to ezetimibe. FDA indicates Food and Drug Administration.

23.2%, and 8.8% lower rate ratio of discontinuation compared with patients over 65 years of age ($P < 0.0001$ for all).

DISCUSSION

In our cohort of ezetimibe users obtained from a national pharmacy benefits manager, we found that almost half were nonpersistent in the first year of use, and rates of nonpersistence increased substantially in the months following an FDA communication that questioned the effectiveness of the medication as well as the associated media attention on the drug's effectiveness. Before the communication, patients who discontinued therapy with ezetimibe changed to a clinically appropriate substitute only about 10% of the time in the 90 days subsequent to discontinuation. After the warning, those rates increased, but patients still switched to an appropriate substitute less than one fifth of the time. These results indicate that, although there was an increase in the proportion of clinically appropriate switching after the FDA communication, there was a substantial increase in the absolute number of patients who discontinued ezetimibe therapy and did not switch to a clinically appropriate alternative after the FDA warning had been communicated.

Extensive evidence demonstrates that hypercholesterolemia is underdiagnosed and substantially undertreated. Only less than half of the patients who require lipid-lowering therapies actually receive them, even among high-risk patients, despite widely accepted guidelines for management and solid evidence to guide therapy.[11–14] Of those who are treated, only about a third achieve the low-density lipoprotein levels established by the accepted guidelines.[15] If patients respond to an FDA communication or unsupportive media attention by discontinuing a cholesterol-lowering medication rather than switch to a more appropriate therapy, the undertreatment problem is exacerbated. These findings raise questions about the way an FDA warning and related media attention should best be communicated to patients and physicians. In the case of ezetimibe, the communication highlighted questions about efficacy but did not recommend discontinuation and did not provide guidance with regard to appropriate substitutes for patients. Subsequent to the communication, rates of discontinuation of ezetimibe increased, and the absolute number of patients who discontinued ezetimibe and did not switch to a clinically appropriate alternative increased substantially. These findings warrant additional study to evaluate whether warnings that provide clinical guidance to doctors and patients will lead to more appropriate therapy rather than bluntly reduce overall rates of treatment.

It is notable that induced discontinuation rates varied by patient characteristics. Lower-income patients, younger patients, and female patients were less likely to discontinue their ezetimibe therapy in response to the FDA communication and media attention. Because of the unclear clinical message regarding ezetimibe, it is not possible to decipher whether lower rates of discontinuation were more or less appropriate for those patients. However, it is essential to

TABLE 2. Estimated Time Trends in Discontinuation of Ezetimibe Before and After the FDA Communication From the Segmented Linear Regression

Time Trends	Rate Difference	Lower 95% CI	Upper 95% CI	*P*
Monthly change before warning	0.000	–0.001	0.001	0.981
Change during transition period	0.057	0.047	0.068	<0.0001
Monthly change after warning	–0.010	–0.013	–0.008	<0.0001

CI indicates confidence interval.

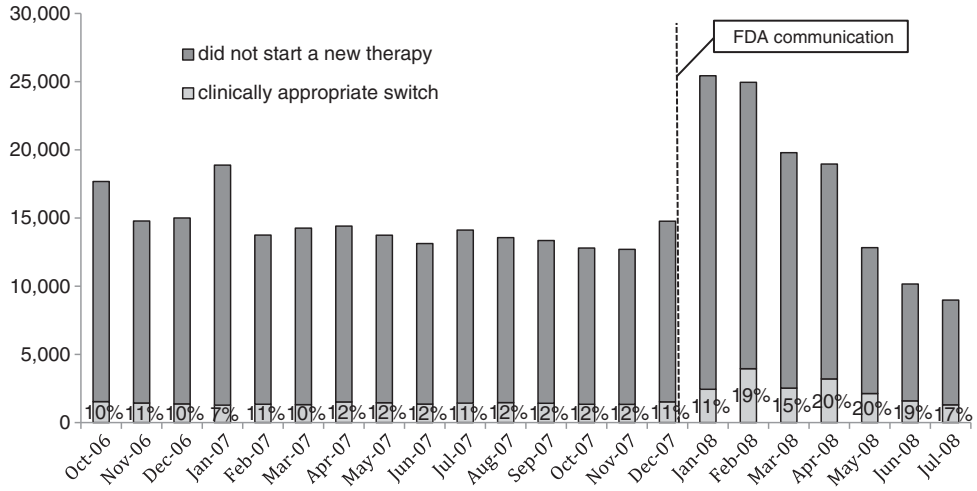

FIGURE 2. Among patients who were nonpersistent to ezetimibe, the proportion of patients who made a clinically appropriate switch. Patients were determined to have made a clinically appropriate switch if, in the 90 days subsequent to ezetimibe discontinuation, they either: (1) added a new cholesterol-lowering medication; or (2) increased the dose of an existing cholesterol medication (one that the patient had filled any time during the study period before becoming nonpersistent to ezetimibe). FDA indicates Food and Drug Administration.

observe that behavioral responses to the dissemination of clinical information occur at varying rates.

Patients receive information about medication safety from a number of sources, and the FDA is only one of them. Patients and physicians may have learned about the questionable efficacy of ezetimibe from a scientific publication in a high-impact medical journal, lay media coverage of that publication, and responses from clinicians and specialty societies.[16–19] Although the results of the trial were not published for several months after the FDA communication, all of these events happened over a short time period, and we were unable to isolate the effects of any particular message on behavior. Using pharmacy claims to determine discontinuation rates, we were unable to determine the specific day that a patient discontinued therapy; rather, we could only determine the date that they ran out of medication. It is quite possible that patients were more likely to respond to information disseminated by the lay press than to the FDA communication, and physicians may have been more responsive to scientific publications. Further study to examine the types of communication that were most likely to influence patient behavior would be informative. Nevertheless, as the nation's regulatory agency for prescription medications, the FDA is expected to play a meaningful role in educating physicians and patients about issues related to the safety and efficacy of medications they regulate and should take some responsibility in helping patients and physicians to interpret new information about a medication's safety and/or efficacy.

Our study is limited by the sample we evaluated. We focused on patients with prescription drug coverage through a large pharmacy benefits manager. Although Medicare and Medicaid beneficiaries were well represented, these results

TABLE 3. Estimated Time Trends in Discontinuation of Ezetimibe and Interactions Between Sex, Income Quintile, and Age Group With the Change in Discontinuation at the FDA Communication From the Fully Adjusted Poisson Model*

	Estimate	Lower 95% CI	Upper 95% CI	*P*
Time trends (RRs)				
Monthly change before warning	1.004	1.003	1.004	<0.0001
Change during the transition period	2.816	2.746	2.888	<0.0001
Monthly change after warning	0.801	0.798	0.804	<0.0001
Interactions between demographics and change during transition period (ratios of RRs)				
Female	0.931	0.917	0.944	<0.0001
Income in zip code quintile 1†	0.870	0.850	0.890	<0.0001
Income in zip code quintile 2†	0.922	0.901	0.944	<0.0001
Income in zip code quintile 3†	0.929	0.907	0.951	<0.0001
Income in zip code quintile 4†	0.945	0.923	0.968	<0.0001
Age 18–34	0.676	0.631	0.725	<0.0001
Age 35–49	0.768	0.750	0.786	<0.0001
Age 50–64	0.912	0.898	0.926	<0.0001

*Adjusting for age group, income quintile, sex, number of unique medications (0–2; 2–5; 5–8; ≥9), indicators for the number of months since the start of treatment (at the patient level), indicators of calendar month (January–December), and linear trends before and after January 2008.

†Income quintile 1: $0–$33,162; income quintile 2: $33,163–$40,194; income quintile 3: $40,195–$48,944; income quintile 4: $48,945–$61,194; income quintile 5: $61,195+.

CI indicates confidence interval.

cannot be generalized to patients without pharmacy insurance. The associations we found between patient characteristics and discontinuation must not be interpreted as causal, and some of the patient characteristics (eg, median income in zip code) may reflect other patient-level characteristics (eg, education) that were unmeasurable with our data source. One might hypothesize that wealthier patients were also more educated and more likely to attend and respond to media coverage about a scientific study or regulatory warning.

We used a rolling cohort with a standard length of cohort entry to allow for the study of time trends in medication use while uncoupling the time-varying nature of medication adherence. However, if the patients who initiated therapy with ezetimibe changed over time in ways associated with adherence behavior, a bias could have been introduced into our analysis. In addition, the communication issued about ezetimibe was somewhat unusual, in that there was no clear signal of harm detected. The signal indicated lack of efficacy on a prespecified outcome, coronary intimal wall thickness. We cannot generalize behavior in response to this particular communication to behavior after warnings that differ in the type of information relayed. Moreover, the reduced rate of discontinuation that followed a peak of discontinuation may be due to "harvesting"—many of the susceptible patients may have discontinued shortly after the FDA warning and media communications, leaving fewer susceptible patients to discontinue in subsequent months.

In conclusion, these findings have implications both for drug regulation and for future research. If a warning leads patients to discontinue a medication without initiating a substitute treatment, then regulators may be well served to evaluate more explicitly the balance between the public health gains from patients stopping a given medication and the public health losses from nontreatment of an important medical condition. In terms of research, studies of nonadherence should move beyond simply documenting nonadherence to evaluate the compensatory actions that patients may take when they stop adhering to a given treatment. A more robust understanding of these processes may lead to more effective public health warnings regarding new data about medications.

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