

Characteristics of Patients Receiving Pharmaceutical Samples and Association Between Sample Receipt and Out-of-Pocket Prescription Costs

G. Caleb Alexander, MD, MS,*†‡§ James Zhang, PhD,*†¶ and Anirban Basu, PhD*‡

Background: Pharmaceutical samples are widely used for promotion and marketing, yet little is known about who receives samples or how their use is associated with patient's prescription costs.

Objective: To examine the characteristics of those receiving samples and the relationship between sample receipt and out-of-pocket prescription costs.

Design, Subjects, and Measures: We divided the 2002–2003 Medical Expenditure Panel Survey, a nationally representative, panel-design longitudinal study, into baseline and analysis periods. We conducted logistic and generalized linear regression analysis of 5709 individuals in the analysis period who did not receive samples during the baseline period. The primary outcome measures were sample receipt and prescription expenditures.

Results: Fourteen percent of individuals received at least 1 sample during the analysis period. On multivariate analyses sample receipt was greater among those who were younger and those not on Medicaid. In generalized linear regressions controlling for demographic characteristics and health care utilization, the predicted 180-day out-of-pocket prescription expenditures were \$178 [standard error (SE), \$3.9] for those never receiving samples. Among those receiving samples, the corresponding out-of-pocket expenditures were \$166 (SE, \$8.9) for periods before sample receipt ($P = 0.16$ for comparison with those not receiving samples), \$244 (SE, \$9.2) for periods during sample receipt ($P < 0.001$ for comparison with periods before sample receipt) and \$212 (SE, \$12.4) for periods following sample receipt ($P = 0.008$ for comparison with periods before sample receipt). Results were qualitatively similar when total prescription costs were examined.

Conclusions: Individuals receiving samples have higher prescription expenditures than their counterparts. These findings suggest that sample recipients remain disproportionately burdened by prescription costs even after sample receipt.

Key Words: pharmaceutical samples, out-of-pocket costs, pharmacoconomics

(*Med Care* 2008;46: 394–402)

The provision of free pharmaceutical samples to patients is a major method of marketing and promotion for the pharmaceutical industry. Nearly \$16 billion was spent on the provision of samples during 2004, twice that spent on direct office detailing to physicians and more than 3-fold the amount spent on direct-to-consumer advertising.¹

There have been widespread debates about the relative advantages and disadvantages of free samples. Extensive commentary, and some research, has been provided both supporting^{2,3} and arguing against^{4–6} the routine use of samples in the office setting. For example, some argue that samples provide economic relief to patients and help physicians to become familiar with new treatments, whereas others argue that as a marketing tool of the pharmaceutical industry, they lead to overuse of newer drugs over their older counterparts and ultimately increase patients' prescription costs. Despite this, little is known about the characteristics of individuals who receive free samples, or the consequences of sample receipt on patients' out-of-pocket prescription costs. Studies that have been conducted have generally been based on surveys of physicians or been limited to 1 clinical setting, rather than examining broader populations of patients or including detailed measures of health care expenditures and utilization.⁷

The effect of sample receipt on prescription expenditures cannot be solved on a theoretical basis alone. If sample receipt was initiated in response to a decline in health status that generates an increased demand for health care, one would expect to see increases in drug expenditures associated with sample receipt. Similarly, if sample receipt is effective as a method of marketing and promotion so that patients continue to use the same branded products that were initially given as samples, then one would again expect to see increases in drug expenditures associated with sample receipt.

From the *Section of General Internal Medicine, Department of Medicine; †MacLean Center for Clinical Medical Ethics; ‡Center for Health and Social Sciences, University of Chicago; and §Department of Pharmacy Practice, University of Illinois at Chicago School of Pharmacy, Chicago, Illinois.

¶Dr. Zhang is now at the School of Pharmacy, Virginia Commonwealth University, Richmond, Virginia.

Supported by career development awards from the Agency for Healthcare Research and Quality (K08 HS15699-01A1, to G.C.A.) and the Robert Wood Johnson Physician Faculty Scholars Program (to G.C.A.).

The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; and preparation, review, or approval of the manuscript for publication.

Reprints: G. Caleb Alexander, MD, MS, The University of Chicago, 5841 S. Maryland, MC 2007, Chicago, IL 60637. E-mail: galexand@uchicago.edu.

Copyright © 2008 by Lippincott Williams & Wilkins
ISSN: 0025-7079/08/4604-0394

On the other hand, if samples serve primarily to substitute for necessary medications, they may lead to decreases in prescription expenditures.

We used the Medical Expenditure Panel Survey (MEPS)⁸ to examine the characteristics of those receiving samples, as well the relationship between sample receipt and out-of-pocket prescription costs. This survey, which provides a nationally representative survey of the U.S. civilian, non-institutionalized population, was particularly valuable because it contains both prescription data as well as detailed economic data regarding individuals' health care expenditures. We hypothesized that the likelihood of sample receipt would vary based on patient's demographic characteristics; for example, those receiving samples would have higher out-of-pocket costs before sample receipt due to greater chronic illness among future sample recipients. Moreover, we also explored specific mechanisms that may be responsible for any observed associations between sample receipt and prescription expenditures.

METHODS

Data

Details of MEPS, which is conducted by the Agency for Healthcare Research and Quality, are available elsewhere.⁸ It consists of a household component, insurer component, and medical provider component. Here, we use data from the household component, which are derived from a stratified multistage area probability design with an oversampling of areas with high proportions of blacks and Hispanics.⁹ For any given year, MEPS includes more than 1 panel of patients. Here, we use the 2002–2003 household component of a single panel (Panel 7) of MEPS subjects. These subjects were followed for 5 “rounds” during 2002–2003. Although the average length of a “round” is 3 months, there is variation in the round length both within and across subjects. During each round, detailed information was collected regarding individual's medical conditions and health care utilization, including the frequency of emergency room, outpatient, and inpatient encounters. Information was also collected regarding subject's demographic characteristics and prescription medication use, including the receipt of any free pharmaceutical sample for any medication; sample receipt was recorded even for those who did not also receive a prescription. Because the average length of a round is 3 months, an individual may receive both a sample and a prescription for the same medicine within 1 round, and MEPS does not measure the total number of samples received for an individual type of medicine. MEPS also includes detailed data on health care expenditures, including the amount as well as whether the expenditures were paid out-of-pocket or by a third party. Information about medical conditions, health care use, and health care expenditures is collected both by self-report and through rigorous data collection from pharmacy and health care provider records.

Analyses

To conduct our analyses, we first divided the longitudinal data into a “baseline period” (survey rounds 1–2) and

“analysis period” (survey rounds 3–5). We included all patients age 18 years or older and excluded patients who received samples during the baseline period to avoid misattribution of their health care expenditures during the analysis period that were really due to sample receipt during the baseline period (“spillover effect”). We also restricted our analysis to those patients who received at least 1 prescription during the entire analysis period. Sample weights were applied for all analyses to account for the complex sampling strategy of MEPS. Standard errors were obtained using 500 clustered bootstrapped replicates. All analyses were done using Stata Version 9 (Stata Corp., College Station, TX).

Predictors of Sample Receipt

We performed bivariate comparisons and multiple logistic regression to compare the demographic characteristics and health care utilization of patients who did not receive any sample with those who received a sample in a round during the analysis period. To explore the effect of these same covariates on the number of prescriptions for which a sample was received, we used negative binomial regression to account for this over-dispersed count data. The negative binomial regression uses a log-link to relate the mean outcome to a vector of covariates and also allows the variance of the outcome to vary more broadly than the more popular Poisson regression. In fact, the latter is a special case of the negative binomial regression. We adjusted for demographic characteristics (age, sex, race, income, education, insurance, marital status and duration of each round), baseline health care utilization (any hospital admission indicator, number of hospital admissions, any outpatient visit indicator, number of outpatient visits, quintiles of drug expenditures, quintiles of out-of-pocket expenditures and duration of baseline period), round-specific utilization (any hospital admission indicator; number of hospital admissions; any outpatient visit indicator; number of outpatient visits; indicators for diabetes, asthma, hypertension, coronary artery disease, cerebrovascular accident, joint pain and arthritis; number of newly discovered conditions during the sample period), and total number of prescriptions used during the corresponding round. All models were tested for lack of fit. If any lack of fit existed, we planned to explore alternate specifications for our regression by incorporating interactions and polynomials of covariates.

Association Between Sample Receipt and Prescription Expenditures

To examine the association between sample receipt and prescription expenditures, we conducted regression analyses using sample receipt as a predictor variable and prescription expenditures as the outcome variable. We conducted separate regressions for out-of-pocket and total prescription expenditures and in both cases adjusted for the same demographic and health care utilization characteristics previously described. In these analyses, because patient-rounds were the unit of analysis, we included indicator variables to represent patient-rounds during the analysis period that either preceded or followed a round in which a sample was received. Thus, we were able to examine expenditures for 4 different types of patient-rounds: (1) patient-rounds for patients who never

received a sample (“control group”), (2) patient-rounds before sample receipt, (3) patient-rounds in which a sample was received, and (4) patient-rounds after sample receipt. Additionally, we used duration of a round as a covariate in our regression analyses. Although the average length of a round was approximately 90 days, subjects could be sampled at any point during a given round, and thus the length of observation of a particular subject varied considerably, both across subjects (for a given round), and within subjects (across rounds). However, to compare adjusted effects across sample receipt rounds versus nonreceipt rounds, we predict these effects conditional on a 180-day period. We used a newly proposed extended estimating equations estimator to model these skewed outcome variables.^{10,11} This extends the traditional generalized linear models where an additional link parameter is estimated from the data to obtain a better model fit. Furthermore, additional parameters in the variance function are also estimated to increase efficiency. In our regression models, we used a variety of goodness of fit tests, including the modified Hosmer-Lemeshow test, the Pregibon link test, and the Pearson correlation test. We also qualitatively assessed whether any systematic bias was present in the distribution of the residuals.

Mechanisms of Association Between Sample Receipt and Expenditures

One reason for an association between sample use and prescription expenditures might be due to “sample-induced demand,” whereby individuals who receive a sample go on to receive a prescription for the same medicine rather than a different medicine or no medicine at all, and thereby sample receipt may lead to increased expenditures.^{12,13} An alternative, or complementary, explanation is that individuals who receive samples may be sicker than those who do not, and therefore sample receipt may be associated with greater prescription expenditures because sample receipt occurs concomitantly with greater health care use that is not caused by sample receipt. We use the term “illness-induced demand” to refer to this possibility.

We conducted additional analyses to better understand how much “sample-induced demand” and “illness-induced demand” could explain our findings. These analyses are exploratory in nature and are limited in discerning the causal association between sample receipt and health care expenditures. First, we compared the number of diseases among sample recipients and nonrecipients during the baseline and analysis periods. To do so, we examined the mean number of chronic diseases among subjects for the chronic diseases that are assessed in MEPS. We hypothesized that if illness-induced demand were present, sample receipt might serve as a marker for reengagement with the health care system and therefore greater diagnosis of previously under-recognized chronic disease. Thus, we wondered whether sample recipients might have fewer or a similar number of chronic diseases as sample nonrecipients at baseline, yet more chronic diseases identified during or following periods of sample receipt. Second, we stratified subjects into quartiles based on their baseline insurance status and health care expenditures. We reasoned that if illness-induced demand were present, those

subjects with low health care expenditures at baseline might have larger increases in expenditures associated with sample receipt, as lower expenditures at baseline might reflect poor health care access rather than good health. In these exploratory analyses, we treated low expenditures as a proxy for better health, recognizing that some subjects with lower expenditures may not actually have better health, but merely lower health care utilization. Third, we compared the likelihood of medication continuation among those receiving a sample and those receiving the same medication without a sample provided. To do so, we first identified individuals receiving a sample during the first round in the analysis period. We then performed a 1:1 match of these individuals with a control patient receiving the same medicine during the same round. In cases where more than 1 control patient was eligible to be matched, we randomly selected 1 individual. Next, we defined our outcome variable as receipt of a prescription for the same medicine during the second round in the analysis period. We then used logistic regression to examine the independent association between different predictor variables and medication continuation. Predictor variables included whether or not the medication was received as a sample in the previous round, as well as the subject demographic and health care utilization characteristics previously described. We reasoned that if sample receipt was influential, the likelihood of medication continuation might be greater among those receiving samples than those receiving a first-time prescription for the same medicine.

RESULTS

Subjects and Pharmaceutical Sample Use

Of the 17,206 patients in the 2002 MEPS who were followed through 2003, 5389 (31%) were excluded due to age less than 18 years, 3995 (23%) were excluded due to having no prescription filled during the analysis period, 1669 (10%) were excluded due to receiving free samples at baseline, and 444 (3%) were excluded due to missing data, resulting in a sample size of 5709 (33%) patients for this study, each of whom were followed for 2 rounds in the baseline period and 3 rounds in the analysis period. These 5709 patients received a total of 2343 samples during the analysis period. Of the 5709 subjects, the mean age was 48 years, 84% were white, and 76% had private insurance (Table 1). The characteristics of these sample recipients are compared with other sample recipients captured by MEPS in the Appendix (Table A1); overall, sample recipients who were excluded were similar to those included in the study, except for they tended to be younger and have a higher prevalence of asthma.

Predictors of Sample Receipt

As depicted in Table 1, those receiving samples were more likely to be female (62% vs. 55%) and white (87% vs. 83%) (P values ≤ 0.01). On multivariate analyses, sample receipt remained associated with many patient characteristics (Table 2). For example, the odds of sample receipt decreased with age [odds ratio (OR), 0.85 per 10-year increase; 95% confidence interval (CI), 0.78–0.92] and income (OR, 0.96 per \$10K increase; CI, 0.93–1.00). Also, patients under Medicaid were significantly less likely to receive a sample

TABLE 1. Characteristics of Sample Recipients and Nonrecipients (N = 5709; Weighted N = 57,108,524)*

	Sample Recipients (n = 7,951,559)	Sample Nonrecipients (n = 49,156,965)
Age, mean (SD), years	48 (17)	48 (18)
Female, thousands (%)	4916 (62)	27,260 (55)
Race, thousands (%)		
White	6895 (87)	40,816 (83)
African American	708 (9)	5506 (11)
Asian	161 (2)	1876 (4)
Other	188 (2)	959 (2)
Ethnicity, (%)		
Hispanic	727 (9)	49,157 (10)
Priority conditions, thousands (%)		
Diabetes mellitus	623 (8)	3653 (7)
Asthma	227 (3)	1618 (3)
High blood pressure	14,271 (29)	2457 (31)
Coronary heart disease	302 (4)	1746 (4)
Stroke	225 (3)	1439 (3)
Emphysema	140 (2)	722 (1)
Joint pain	3464 (44)	18,683 (38)
Arthritis	2262 (28)	11,322 (23)
Education, thousands, (%)		
High school or less	4035 (51)	25,524 (52)
Some college	2043 (26)	10,706 (22)
College degree	1086 (14)	7896 (16)
Professional or graduate degree	787 (10)	5031 (10)
Insurance status, [†] thousands (%)		
Private or employer purchased	5986 (75)	37,430 (76)
Medicare	1854 (23)	10,312 (21)
Medicaid	601 (8)	5049 (10)
Uninsured	640 (8)	3861 (8)
Annual income, mean (SD), \$	29,251 (27,506)	31,157 (29,989)
Out-of-pocket prescription costs, [‡] mean (SD), \$	235 (451)	218 (508)
Samples dispensed, mean (SD)	2.7 (4.9)	0
Total prescriptions dispensed, [‡] N (SD)	9.8 (14.4)	9.5 (14.1)
Unique medicines dispensed, [‡] N (SD)	3.1 (3.7)	2.8 (3.0)

*All comparisons statistically significant ($P < 0.001$).

[†]Subjects may have more than one type of insurance.

[‡]Estimates limited to baseline period (rounds 1 and 2).

compared with those without insurance (OR, 0.60; CI, 0.44–0.82). Finally, there was no statistically significant association toward greater likelihood of sample receipt with greater baseline out-of-pocket prescription costs. Some, but not all, of these associations persisted in analyses examining the total number of samples received (Table 2).

Effect of Sample Receipt on Prescription Expenditures

Figure 1A presents the effect of sample receipt on out-of-pocket and total prescription expenditures after con-

trolling for potentially confounding variables. Among those never receiving a sample, the average out-of-pocket prescription expenditure per survey round (predictions were made conditional on 180 days as the duration of a round) was approximately \$178 [standard error (SE), \$3.9]. Among those receiving a sample, the corresponding out-of-pocket expenditure during rounds before sample receipt was similar, \$166 (SE, \$8.9) (\$166 vs. \$178; P value = 0.16). By contrast, during rounds when samples were received, these subject's out-of-pocket prescription costs were on average approximately \$66 (SE, \$8.6) greater than the costs of those not receiving samples (\$244 vs. \$178; P value < 0.001). Out of-pocket expenditures declined somewhat, but not to presample period levels, during rounds following sample receipt.

A similar pattern was observed when examining the association between sample receipt and total, rather than out-of-pocket, pharmaceutical expenditures (Fig. 1B). In each regression, groups of variables jointly representative of subject demographics, baseline health care utilization, and round-specific utilization were each significantly associated with out-of-pocket and total prescription expenditures. Our models achieved an R^2 of about 0.30 in the raw-scale outcomes.

None of the goodness of fit tests was statistically significant, and none showed any substantive bias in predictions. For example, the Pearson correlations coefficients for all our regressions were less than 0.05 and P values were well over 0.20. All model fits seemed to track the observed outcome well.

Exploratory Analyses of Association Between Sample Receipt and Expenditures

Table 3 demonstrates that unadjusted disease prevalence was greater among sample recipients than nonrecipients at baseline (1.22 vs. 1.09) and during follow-up (1.44 vs. 1.18). After accounting for the increasing morbidity among all subjects over the time course of the study, sample recipients remained more likely than nonrecipients to have a chronic disease, with a mean difference in disease prevalence of 0.12 ($P < 0.001$). Table A2 (Appendix) depicts the unadjusted association between sample use and expenditures stratified by subjects' baseline insurance status. Overall, subjects in the lowest quartile of baseline out-of-pocket expenditures experienced the greatest increase in expenditures associated with sample use, whereas subjects in the highest quartiles experienced much more modest changes. These patterns differed somewhat by subjects' baseline insurance status.

Likelihood of Medication Continuation Based on Sample Receipt

Of 136 subjects who received a sample for one or more prescriptions during the first analysis round, 99 (73%) could be matched to a similar subject who received the same combination of prescriptions during the same round. Of these, 24 subjects were excluded due to continuing to receive a sample during subsequent rounds. Of the remaining 75 matched pairs, on bivariate analysis, rates of continuation of a drug were lower among those receiving a sample (19% continued medicine as a prescription during subsequent

TABLE 2. Multivariate Association Between Subject Characteristics, Health Care Utilization, and Pharmaceutical Sample Receipt (N = 5709)

Covariates	Any Sample Odds Ratio (95% CI)*	No. Prescriptions for Which Sample Received IRR (95% CI)†
Age (per 10 yr increase)	0.85 (0.78–0.92)	0.87 (0.79–0.96)
Income (per \$10,000 increase)	0.96 (0.93–1)	0.96 (0.92–0.99)
Race		
White/other	Referent	Referent
Black	0.86 (0.65–1.13)	1.06 (0.76–1.47)
Asian	0.84 (0.5–1.42)	0.7 (0.39–1.23)
Ethnicity		
Non-Hispanic	Referent	Referent
Hispanic	0.99 (0.75–1.32)	0.88 (0.66–1.16)
Education		
High school or less	Referent	Referent
Some college	0.84 (0.61–1.16)	0.75 (0.53–1.07)
College degree	0.96 (0.68–1.34)	0.97 (0.68–1.37)
Professional or graduate degree	0.81 (0.56–1.18)	0.71 (0.48–1.06)
Sex		
Male	Referent	Referent
Female	1.14 (0.95–1.37)	1.09 (0.88–1.35)
Marital status		
Single/divorced/widowed/separated	Referent	Referent
Married	1.09 (0.9–1.33)	0.94 (0.75–1.17)
Current round duration (days)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Family size (per additional person)	0.95 (0.92–0.99)	0.98 (0.95–1.02)
Insurance		
No insurance	Referent	Referent
Private insurance	0.93 (0.74–1.17)	0.8 (0.62–1.04)
Medicaid	0.60 (0.44–0.82)	0.57 (0.39–0.84)
Medicare	1.21 (0.89–1.65)	1.11 (0.78–1.57)
Baseline Period Variables		
Baseline period duration (days)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Any outpatient visit	1.05 (0.81–1.37)	0.94 (0.69–1.28)
Any hospital admission	0.75 (0.43–1.33)	1.81 (0.78–4.23)
No. outpatient visits	1.00 (0.98–1.02)	0.99 (0.97–1.01)
No. hospital admissions	1.00 (0.67–1.51)	1.82 (0.94–3.53)
Baseline total drug expenditures		
First quintile	Referent	Referent
Second quintile	0.47 (0.18–1.24)	0.87 (0.37–2.06)
Third quintile	0.39 (0.15–0.98)	1 (0.42–2.41)
Fourth quintile	0.32 (0.12–0.83)	0.98 (0.38–2.5)
Fifth quintile	0.32 (0.12–0.84)	0.7 (0.27–1.82)
Baseline out-of-pocket drug expenditures		
First quintile	Referent	Referent
Second quintile	0.99 (0.38–2.59)	0.64 (0.27–1.51)
Third quintile	0.94 (0.37–2.37)	0.69 (0.29–1.63)
Fourth quintile	1.09 (0.43–2.76)	0.65 (0.27–1.56)
Fifth quintile	1.41 (0.56–3.6)	0.96 (0.38–2.41)

Covariates	Any Sample Odds Ratio (95% CI)*	No. Prescriptions for Which Sample Received IRR (95% CI)†
Current Round Variables		
Diabetes		
No	Referent	Referent
Yes	1.14 (0.83–1.57)	1.19 (0.82–1.72)
Asthma		
No	Referent	Referent
Yes	1.01 (0.72–1.42)	0.85 (0.59–1.22)
Hypertension		
No	Referent	Referent
Yes	1.15 (0.93–1.42)	1.04 (0.82–1.33)
Coronary heart disease		
No	Referent	Referent
Yes	0.89 (0.56–1.41)	0.51 (0.29–0.92)
Cerebrovascular accident		
No	Referent	Referent
Yes	1.37 (0.84–2.22)	1.23 (0.71–2.14)
Joint pain		
No	Referent	Referent
Yes	1.26 (1.03–1.54)	1.29 (1.03–1.6)
Arthritis		
No	Referent	Referent
Yes	1.3 (1.04–1.64)	1.18 (0.91–1.52)
Any outpatient visit	0.49 (0.38–0.64)	0.34 (0.25–0.44)
Any hospital admission	1.20 (0.66–2.21)	0.63 (0.25–1.63)
No. outpatient visits	0.91 (0.59–1.41)	0.63 (0.35–1.14)
No. hospital admissions	1.01 (1.01–1.02)	1.02 (1–1.03)
Total no. prescriptions (per 5 rx increase)	0.97 (0.92–1.02)	1.29 (1.21–1.39)

*Odds ratios derived using logistic regression treating sample rounds as those rounds where sample was received.

†IRR indicates incident rate ratio; IRR derived using negative binomial regression based on total number of samples received.

Bold indicates statistically significant ($P < 0.05$).

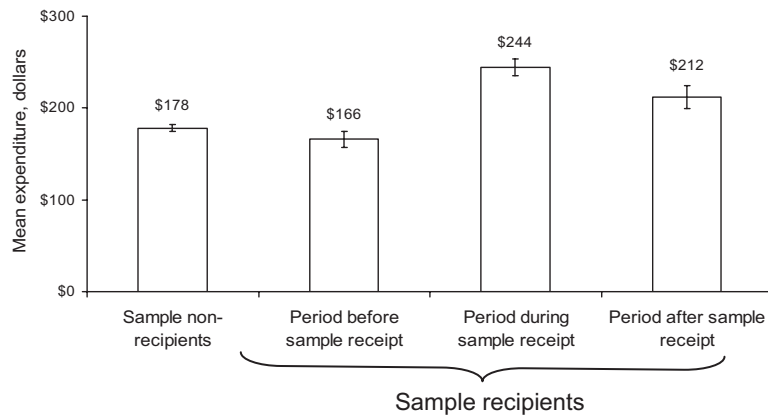
round) than among those receiving a prescription (45% continued medicine). On multivariate analysis, after controlling for demographic and baseline utilization measures, the odds of continuing on the same medication remained considerably lower after sample receipt than after receipt of a prescription for the same medicine (OR, 0.22; CI, 0.08–0.65).

DISCUSSION

In this nationally representative longitudinal study, we found differences in the likelihood of pharmaceutical sample receipt based on patient's age, income, and insurance status. This was not surprising, because the characteristics of patients seen by physicians who dispense samples probably differ from the characteristics of patients seen by physicians who do not, and physician dispensing of samples likely also varies based on patient request and physician discretion, which may in turn be associated with other patient characteristics (eg, number and type of comorbid conditions).

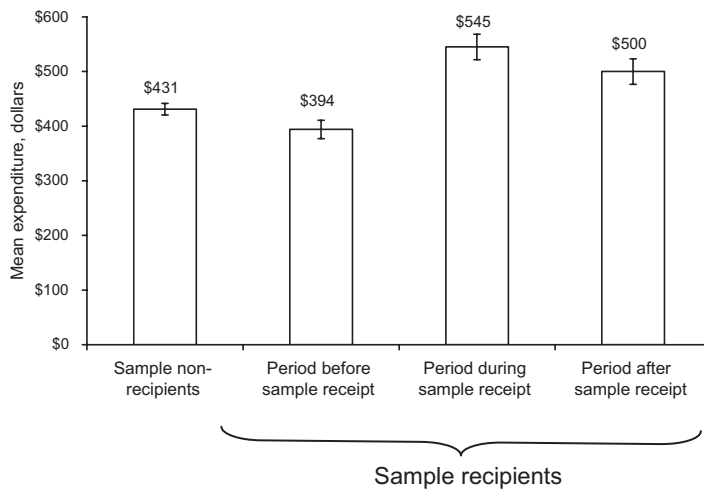
We also found that subjects receiving samples had considerably higher prescription expenditures than those who

A Adjusted association between pharmaceutical sample receipt and out-of-pocket prescription drug expenditures (n = 5709).*



* Prediction for all rounds based on 180 day duration; all models adjusted for subject demographic characteristics ($df = 15, \chi^2 = 256, P < 0.0001$), baseline health care utilization ($df = 5, \chi^2 = 7.6, P = 0.18$), additional baseline utilization ($df = 8, \chi^2 = 822, P < 0.0001$), and round-specific health care utilization ($df = 11, \chi^2 = 313, P < 0.0001$).

B Adjusted association between pharmaceutical sample receipt and total prescription drug expenditures (n = 5709).*



* Prediction for all rounds based on 180 day duration; all models adjusted for subject demographic characteristics ($df = 15, \chi^2 = 274, P < 0.0001$), baseline health care utilization ($df = 5, \chi^2 = 3.1, P = 0.67$), additional baseline utilization ($df = 8, \chi^2 = 1266, P < 0.0001$), and round-specific health care utilization ($df = 11, \chi^2 = 44, P < 0.0001$).

FIGURE 1.

did not, and that these expenditures decreased, but not back to prior baseline, after sample receipt.

A major strength of our study is that unlike most other studies examining sample use, ours included rigorously collected nationally representative longitudinal data on both sample receipt and pharmaceutical expenditures. However, our study also had a number of limitations. Our study was not designed to discern the mechanism that accounts for the associations that we describe. Both “sample-induced demand” and “illness-induced demand” (greater unmeasured illness among sample recipients) are plausible mechanisms that could contribute to our results and our exploratory analyses provide some support for each. For example, our finding that the odds of continuing a medicine was lower with sample receipt than with a prescription for the same medicine

suggests the absence of strong sample-induced demand; however, there may be unmeasured, and immeasurable, differences between sample users and nonusers that make interpretation of these findings difficult. Some of our exploratory analyses supported the presence of greater illness among sample recipients. However, our adjustments for patient’s baseline and current health care utilization only led to a 15–30% decrease in the estimated effect of sample receipt on patient’s prescription expenditures, suggesting that patient’s underlying health care status, or proxies for health status, are only responsible for explaining a small part of the incremental out-of-pocket and prescription expenditures associated with sample receipt among this population. Nevertheless, sample receipt may still be a marker for greater unmeasured illness among sample recipients, and an acute unmeasured

TABLE 3. Comparison of Disease Prevalence Among Sample Recipients and Nonrecipients for Eight Chronic Disease Categories Captured by the Medical Expenditure Panel Survey

	Mean No. Diseases (SD)
Control patients	
During baseline period	1.09 (1.22)
During follow-up period	1.18 (1.28)
Sample patients	
During baseline period	1.22 (1.29)
During follow-up period	1.44 (1.39)
Difference in mean number of diseases during follow-up compared with baseline	0.095*
Difference in mean number of diseases among sample recipients compared with nonrecipients	0.132*
Difference in mean number of diseases among sample recipients compared with nonrecipients during follow-up compared with baseline	0.120*

* $P < 0.001$.

worsening of health status could reasonably explain both increased expenditures as well as sample receipt. Although instrumental variable analysis might help to address this limitation, the challenge of identifying a clean instrument for sample receipt in this data is formidable and remains an area of interest for future analyses.¹⁴ Our results may also be subject to selection bias in so far as the sample recipients we examined may differ from other sample recipients in ways that are associated with their prescription expenditures. We examined for evidence of this in the Appendix (Table A2), which suggested that sample recipients that we examined were similar to other sample recipients that were excluded from our analyses. Finally, our findings could be biased if the accurate ascertainment of sample use was associated with prescription expenditures (eg, individuals with higher expenditures might be more likely to accurately recall sample receipt).

Our findings provide an important complement to a large literature on free pharmaceutical sample use. This is because most published literature on samples takes the form of commentaries,^{2,3} single-site studies,^{4,5} or surveys of attitudes or beliefs without corresponding assessment of sample receipt and expenditures.⁷ These prior reports highlight how complex the issues are related to sample use, including many of the arguments for and against their regular use in clinical practice as described above. However, prior reports have not used nationally representative data to examine who receives samples or how sample use may be associated with out-of-pocket and total prescription expenditures.

For policy-makers and researchers, our findings provide an opportunity to consider the complexity of issues raised by sample use. Many unanswered questions remain. One set of questions pertains to the overall marketing and promotional effect of sample use. For example, how much do lessons from other settings (eg, how household product samples can lead to greater brand loyalty^{15,16}) yield lessons that

are also applicable to pharmaceutical samples¹⁷? To what degree do samples lead to: (1) earlier use of a given brand, (2) substitution of prescriptions that would otherwise be purchased, and (3) expansion of use by patients who would otherwise not use the brand¹⁵? Individual institutions are faced with a second set of vexing questions. For example, what is the impact of prohibiting or limiting free samples on patient's prescription drug utilization, expenditures, and health outcomes, and how can samples be targeted within an institution to patients who will benefit most from their use? Some studies examine these latter issues at single sites⁷; nevertheless, further work is needed to delineate these impacts across broader groups of patients, clinicians, and health care settings.

Although future research may help to answer these and other questions related to sample use, our findings still carry an important implication for patients, clinicians, and policy-makers given how commonly samples are used to assist patients who are burdened by their prescription costs.¹⁸ Our results demonstrate patients receiving free samples have significantly higher out-of-pocket prescription costs than their counterparts who do not receive free samples. If this is due primarily to enhanced brand loyalty induced by sample receipt, then it may have welfare reducing effects on sample recipients due to the forgone alternatives to the sampled drug that are never used. On the other hand, if this result is primarily driven by greater illness-related demand among sample recipients, then it is noteworthy that sample recipients' out-of-pocket prescription expenditures are not lower. Thus, regardless of the degree to which these different mechanisms account for our findings, patients and physicians should consider other complementary ways to reduce patients' burden from out-of-pocket prescription costs.¹⁹

CONCLUSIONS

To our knowledge, this is the first study using rigorously collected longitudinal data to examine the association between pharmaceutical sample use and patient's prescription expenditures. Although free pharmaceutical samples may provide many patients with valuable short-term economic relief, our results highlight the economic burden that persists for patients who receive pharmaceutical samples, both during and following periods of sample receipt.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Martin Zelder for assistance with study design and Randall Stafford, David Meltzer, and Sam Zuvekas for helpful comments on earlier manuscript drafts. Dr. Alexander 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.

REFERENCES

1. Prescription drug trends. Kaiser Family Foundation. November 2005. Fact Sheet 3057-04.
2. Wolf BL. Drug samples: benefit or bait? *JAMA*. 1998;279:1698-1699.
3. Holmer AF. Industry strongly supports continuing medical education. *JAMA*. 2001;285:2012-2014.

4. Christie JD, Rosen IM, Bellini LM, et al. Prescription drug use and self-prescription among resident physicians. *JAMA*. 1998;280:1253–1255.
5. Boltri JM, Gordon ER, Vogel RL. Effect of antihypertensive samples on physician prescribing patterns. *Fam Med*. 2002;34:729–731.
6. Backer EL, Von Tonder RJN, Crabtree BF. The value of pharmaceutical representative visits and medication samples in community-based family practices. *J Fam Practice*. 2000;49:811–816.
7. Groves KE, Sketris I, Tett SE. Prescription drug samples—does this marketing strategy counteract policies for quality use of medicines? *J Clin Pharm Ther*. 2003;28:259–271.
8. Medical Expenditure Panel Survey (MEPS). Available at: <http://www.meps.ahrq.gov/>. Accessed on May 19, 2006.
9. Cohen J. Design and methods of the Medical Expenditure Panel Survey Household Component. Rockville, MD: Agency for Health Care Policy and Research; 1997. MEPS Methodology Report No. 1. AHRQ Pub. No. 97-0026.
10. Basu A, Rathouz P. Estimating marginal and incremental effects on health outcomes using flexible link and variance-function parameters. *Biostatistics*. 2005;6:93–109.
11. Basu A, Arondekar BV, Rathouz P. Scale of interest versus scale of estimation: comparing alternative estimators for the incremental costs of a comorbidity. *Health Econ*. 2006;15:1091–1107.
12. Hurwitz MA, Caves RE. Persuasion or information? Promotion and the shares of brand name and generic pharmaceuticals. *J Law Econ*. 1988; 31:299–320.
13. Rizzo RA. Advertising and competition in the ethical pharmaceutical industry: the case of antihypertensive drugs. *J Law Econ*. 1999;42:89–116.
14. Bound J, Jaeger DA, Baker RM. Problems with instrumental variables estimation when the correlation between the instruments and the endogenous explanatory variables is weak. *J Am Stat Assoc*. 1995;90:443–450.
15. Bawa K, Shoemaker R. The effect of free sample promotions on incremental brand sales. *Mark Sci*. 2004;23:345–363.
16. Urban G, Hauser J. *Design and Marketing of New Products*. Englewood Cliffs, NJ: Prentice Hall; 1993:341–342.
17. Gonul FF, Carter F, Petrova E, et al. Promotion of prescription drugs and its impact on physicians' choice behavior. *J Mark*. 2001;65:79–90.
18. Alexander GC, Casalino LP, Meltzer DO. Physician strategies to reduce patients' out-of-pocket prescription costs. *Arch Intern Med*. 2005;165: 633–636.
19. Alexander GC, Tseng CW. Strategies to identify and assist patients burdened by out-of-pocket prescription costs. *Cleve Clin J Med*. 2004; 71:433–437.

APPENDIX

TABLE A1. Characteristics of Included and Excluded Sample Recipients in MEPS 2003 (Weighted)

	MEPS Panel 7 Sample Recipients Included in Analysis (N = 7,951,559)	MEPS Panel 7 Sample Recipients Excluded Due to Sample Receipt During Baseline (N = 8,280,641)	MEPS Panel 8 Sample Recipients Excluded Due to Presence in Panel 8 (N = 19,064,333)
Age, mean (SD), years	48 (17)	42 (24)	45 (22)
Female, thousands, (%)	4916 (62)	5245 (63)	12,030 (63)
Race, thousands, (%)			
White	6895 (87)	7176 (87)	16,463 (86)
African American	708 (9)	748 (9)	1576 (8)
Asian	161 (2)	163 (2)	532 (3)
Other	188 (2)	194 (2)	493 (3)
Ethnicity, (%)			
Hispanic	727 (9)	553 (7)	1203 (6)
Priority conditions, thousands, (%)			
Diabetes mellitus	623 (8)	817 (10)	1616 (8)
Asthma	227 (3)	1139 (14)	2168 (11)
High blood pressure	14,271 (29)	2789 (34)	6147 (32)
Coronary heart disease	302 (4)	372 (5)	847 (4)
Stroke	225 (3)	389 (5)	817 (4)
Emphysema	140 (2)	225 (3)	467 (3)
Joint pain	3464 (44)	3268 (39)	8197 (43)
Arthritis	2262 (28)	2662 (32)	5916 (31)
Education, thousands, (%)			
High school or less	4035 (51)	4826 (63)	9902 (54)
Some college	2043 (26)	1411 (18)	3976 (22)
College degree	1086 (14)	779 (10)	2609 (14)
Professional or graduate degree	787 (10)	615 (8)	1885 (10)
Insurance status,* thousands, (%)			
Private or employer purchased	5986 (75)	6117 (74)	14,119 (74)
Medicare	1854 (23)	2038 (25)	4452 (23)
Medicaid	601 (8)	1016 (12)	1775 (9)
Uninsured	640 (8)	640 (8)	1633 (9)
Annual income, mean (SD), \$	29,251 (27,506)	21,230 (26,471)	26,871 (28,659)

*Subjects may have more than one type of insurance.

TABLE A2. Unadjusted Association Between Sample Use and Expenditures Stratified by Baseline Insurance Status

	Out-of-Pocket Expenditures During Analysis Period Mean (SD)			
	First (Lowest) Quartile	Second Quartile	Third Quartile	Fourth (Highest) Quartile
Baseline Medicare coverage				
Control patients	139 (272)	198 (300)	236 (444)	654 (836)
Sample patients during rounds before sample received	43 (37)	139 (57)	229 (119)	1037 (316)
Sample patients during rounds when sample received	103 (135)	241 (263)	531 (479)	769 (775)
Sample patients during rounds after sample received	341 (421)	259 (205)	553 (492)	806 (820)
Baseline Medicaid coverage				
Control patients	67 (189)	99 (237)	150 (283)	316 (530)
Sample patients during rounds before sample received	5 (7)	23 (19)	81 (82)	444 (493)
Sample patients during rounds when sample received	54 (105)	180 (182)	236 (355)	579 (577)
Sample patients during rounds after sample received	25 (41)	155 (126)	309 (305)	485 (651)
Baseline private insurance coverage				
Control patients	58 (110)	87 (146)	152 (207)	336 (446)
Sample patients during rounds before sample received	7 (4)	33 (20)	147 (70)	464 (368)
Sample patients during rounds when sample received	90 (176)	131 (206)	199 (214)	415 (410)
Sample patients during rounds after sample received	136 (225)	163 (276)	271 (317)	406 (497)