HHS Public Access

Author manuscript

Drug Saf. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

Drug Saf. 2016 March ; 39(3): 261–270. doi:10.1007/s40264-015-0382-9.

Use of Prescription Drug Samples in the USA: A Descriptive Study with Considerations for Pharmacoepidemiology

Christian Hampp[1], **Patty Greene**[2], and **Simone P. Pinheiro**[1]

[1]Division of Epidemiology-I, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA

[2]Division of Epidemiology-II, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

Abstract

Introduction—Free prescription drug samples provided in physician offices can lead to exposure misclassification in pharmacoepidemiologic studies that rely on pharmacy claims data.

Methods—We quantified drug-specific sample provision rates based on nationally projected data from a survey of over 3200 US office-based physicians for 1993–2013.

Results—Between 2009 and 2013, a total of 44.7 % of newly initiated brand-only sitagliptin but only 3.6 % of generically available metformin therapy was provided as samples. We observed similar discrepancies between newly initiated rosuvastatin and simvastatin, dabigatran and warfarin, atomoxetine and methylphenidate, and between oral antibiotic drugs. During continued therapy, sample use was still present though to a lesser extent (sitagliptin 17.0 %, rosuvastatin 23.9 %), and remained high for some oral contraceptives (norethindrone 55.8 %). Oral contraceptives had the longest average days of sample supply (levonorgestrel, continued use 85.1 days). The average days of supply for all other chronically used study drugs ranged from 13.4 (dabigatran, new use) to 25.3 (exenatide, continued use) per sample provided. From 1993 to 2013, we found pronounced drops in sample provisions over time coinciding with more recent generic approval dates.

Conclusions—We observed markedly differential exposure to medication samples between branded and generic drugs. This can introduce bias in pharmacoepidemiologic studies, especially when adverse events that occur soon after drug initiation are of interest.

Christian Hampp christian.hampp@fda.hhs.gov.

Compliance with Ethical Standards

Conflict of interest Christian Hampp, Patty Greene, and Simone Pinheiro have no conflicts of interest that are directly relevant to the content of this study

Ethical standards The study was exempted from review by the FDA Research Involving Human Subjects (RIHSC) committee under 45 CFR 46 101(b)(4).

1 Introduction

In retrospective studies that evaluate associations between drug exposure and outcomes of interest, pharmacoepidemiologists often rely on pharmacy claims data to ascertain drug exposure. Pharmacy claims are generated when patients obtain medications from a pharmacist and the pharmacy bills a third-party payer. Yet, patients can obtain drugs, including prescription medications, through other mechanisms, resulting in exposures that may not be apparent in pharmacy claims data. These include drugs purchased entirely out of pocket, such as over-the-counter medications, low-cost ($US 4) generics [1], drugs not listed on the payer's formulary, and those obtained by patients who lack insurance benefits for prescription drugs. Drugs obtained outside the pharmacy will likewise not result in a pharmacy claim. These include illicit purchases, drugs obtained from other patients—including family members, drugs imported from other countries, and free prescription drug samples provided to a patient in a physician's office. In the USA, the pharmaceutical industry uses free samples as a marketing tool to familiarize prescribers with the drug. The impact of samples on prescriber behavior and cost to patients and the US healthcare system have been widely researched and discussed [2–10].

Sample use and the resulting under-ascertainment of exposure can introduce bias in pharmacoepidemiologic studies. This can be the case especially when undetected sample use is differential between study cohorts, when sample recipients' characteristics differ from patients who do not receive samples [11, 12], when it results in misattribution of early drug effects, or when it results in the inadvertent selection of prevalent users instead of new users of a drug. Only few studies have investigated the implications of sample use on pharmacy claims-based research [13, 14] despite recommendations that investigators estimate the extent of exposure misclassification in their studies and conduct sensitivity analyses to quantify the potential bias resulting from sample use. One challenge to researchers is the inherent difficulty of estimating the extent of sample use in their pharmacy claims data. Instead, several studies attempted to quantify the use of samples in the aggregate using alternative databases [11, 12, 15] and for specific drugs or drug classes [16, 17] using innovative, indirect approaches.

In the USA, pharmacoepidemiologic studies are often conducted in databases that are limited to a particular payer type, such as commercial insurance and the public programs, Medicaid and Medicare. Because each of these programs has distinct patient and reimbursement characteristics, the use of samples may differ between them. In addition, the use of samples may differ between drug classes and between drugs within a class, depending on their patent status. We conducted this descriptive study of sample provisions in various therapeutic areas and payer types to help researchers understand the extent of sample use most applicable to their own study settings.

2 Methods

2.1 Study Drugs

Study drugs were selected to exemplify scenarios in which undetected, differential sample use could introduce bias. We expected this to be the case when extensively marketed

branded drugs are compared with generically available drugs with the same or similar indications. To maximize statistical precision, we selected commonly used medications with chronic indications, including diabetes, hyperlipidemia, hypertension, anticoagulation, attention-deficit/hyperactivity disorder, and contraception. In addition, we selected oral and ophthalmic antibiotics to investigate the use of samples in short-term therapy, which typically does not last longer than 5–21 days for most types of infection [18, 19]. The chronically used drugs do not carry a recommendation that limits therapy duration.

2.2 Data Source

We extracted information on sample use from the Encuity Research Treatment Answers database. This database includes data from a survey of over 3200 office-based physicians representing 30 specialties across all 50 US states and the District of Columbia who report on all patient activity during 1 typical workday per month. Physicians are recruited by region and specialty based on the American Medical Association masterfile, which includes member and nonmember physicians. For each patient visit, physicians complete an encounter form, which collects patient characteristics, diagnoses, and the patient's drug therapy. Information on drug therapy includes all of the patient's drugs of which the physician is aware, regardless of the issuance of a prescription at the respective visit. When physicians mention a drug, they are asked to specify whether samples of the drug were provided during this visit, a prescription for the drug was issued, neither, or both. In addition, physicians indicate for each drug whether it is newly initiated—that is, prescribed to a patient who had not been using the drug for this episode of care—or a continuation of previous therapy with that drug. This determination is made independently from concomitant therapy for the same or other indications. For example, during a visit when a physician adds sitagliptin to a patient's ongoing metformin therapy, both drugs would be indicated on the encounter form for that visit; sitagliptin would be considered new therapy and metformin would be considered continued therapy.

2.3 Analytic Approach

In our analysis, we estimated the proportion of sample provisions for each study drug as the nationally projected number of office visits where a sample was provided for that drug divided by the nationally projected number of office visits where either a prescription was issued for that drug, a sample was provided, or both. Concomitant study drugs within individual patients were treated independently. For example, a patient who received a sample for sitagliptin and a prescription for metformin during the same visit contributed to the denominators of both drugs, but only to the numerator of sitagliptin in the calculation of the proportion of sample provisions.

All data are nationally projected by the data vendor, who weighs each survey according to how many workdays it represents in a given specialty for a given geographic region. However, projected counts of fewer than 100,000 drug mentions are based on few observed visits and are considered statistically unstable. Projected drug sample counts of fewer than 100,000 drug mentions can occur either when the overall frequency of drug mentions is common but the proportion of sample provision is small, or when the overall use of the drug is uncommon, regardless of the proportion of sample provision. To provide useful

information while accounting for uncertainty, we did not display estimates based on fewer than 100,000 projected counts, but indicated whether the projected proportion of sample use was less than or greater than 3.0 %. The nature of the data provided to us did not enable us to calculate confidence intervals for proportions of sample provisions.

We conducted three separate analyses. In the first analysis, we extracted drug-specific proportions of sample provision for selected drugs that are part of the aforementioned therapeutic areas. We applied an observation period of 5 years, from 2009 through 2013, to emulate hypothetical study scenarios based on recent data. In the second analysis, we extracted annual rates of sample use for all study drugs from 1993 through 2013 to observe longitudinal trends and changes in trends around the times of first availability as generic drugs. In the third analysis, we extracted more detailed survey data on sample use for study drugs with the highest projected sample use to further describe sample provisions. These data included samples provided together or not together with a prescription for the same drug at the same visit, the average days of supply included in each sample provision and the proportion of sample use by type of insurance benefit. We conducted this analysis with aggregated data from the last 5 calendar years that preceded the year of generic approval. This period spanned from 2009 through 2013 for all study drugs except losartan, norethindrone, and drospirenone, for which we extracted data from 2005 through 2009, from 2006 through 2010, and from 2008 through 2012, respectively.

3 Results

3.1 Sample Use Among Drug Initiators

Our analyses showed a substantial proportion of sample use among initiators of most studied drugs, with a markedly different extent of sample use between newer, brand-only drugs compared with established, generically available drugs within various therapeutic areas, using aggregated data from 2009 through 2013 (Table 1). For instance, samples were provided during 44.7 % of visits where sitagliptin was first prescribed to a patient, a sample was provided, or both. Sitagliptin is an antidiabetic medication approved in 2006 and is only available as a branded drug. The respective proportion was only 3.6 % for metformin, an antidiabetic medication for which generic versions have been available since 2002. We observed similar discrepancies between newer and established medications in other drug classes, including the anti-hyperlipidemic drugs rosuvastatin and simvastatin, the anti-coagulants dabigatran and warfarin, and the psychiatric medications atomoxetine and methylphenidate. The discrepancies were less pronounced among the studied antihypertensive drugs; however, the branded drug, losartan, was available as a generic drug for a large part of the 5-year observation period. Differential rates of sample use between newer and established medications also existed among antibiotic drugs that are used for acute illnesses. New use of moxifloxacin, the oral antibiotic most recently approved among the studied oral antibiotics, had the highest rates of sample use among oral antibiotics (24.3 %). However, among select ophthalmic antibiotics, sample use of levofloxacin was highest (40.1 %) even when compared with more recently approved moxifloxacin (14.0 %). The proportion of sample use was substantial among the studied contraceptives, ranging from 20.3 to 75.3 % among initiators of the drugs. Unexpectedly, during the 5-year observation

period, norethindrone/ethinyl estradiol (EE)/ferrous fumarate (fe), the oral contraceptive with the earliest approval date of the select oral contraceptives, had the highest proportion of sample use (75.3 %, Table 1).

3.2 Sample Use During Continued Therapy

Sample use was less prevalent during continued therapy, but differences within therapeutic areas still existed. For instance, sample use during continued therapy ranged from 1.2 % for metformin to 17.0 % for sitagliptin among antidiabetic drugs and from 1.1 % for simvastatin to 23.9 % for rosuvastatin among antihyperlipidemic drugs. Because antibiotic therapy is usually short in duration, data on sample use were scarce for continued therapy. Among oral contraceptive drugs, sample use was somewhat less frequent during continued therapy compared with newly initiated therapy, but remained substantial, ranging from 11.5 % for products that contain norgestimate to 55.8 % for products that contain norethindrone (Table 1).

3.3 Longitudinal Patterns of Sample Use

We evaluated annual rates of sample use for all study drugs from 1993 through 2013. Figure 1 illustrates trends in the proportion of samples provided with new use for selected antidiabetic, antihyperlipidemic, antihypertensive, and oral contraceptive drugs. Approval dates of generic versions are indicated when applicable. Among drugs with earlier generic approval dates, such as glipizide and metformin, a long-term downward trend in sample use was present; however, no noticeable change occurred around the time of generic approval. In contrast, drugs with more recent generic approval dates, including pravastatin, simvastatin, atorvastatin, enalapril, amlodipine, and losartan, experienced pronounced drops in sample use, to an extent of practical disappearance of samples at the time around or just after the approval of generic versions of each drug. All studied oral contraceptive drugs had historically high levels of sample use for newly initiated therapy, often exceeding 75 %; however, for products that contain norgestimate or levonorgestrel, sample use started to decline well before the availability of generic versions in 2011 and continued to decline thereafter. In contrast, sample use remains high for products that contain norethindrone or drospirenone, despite the recent approval of generic versions. In 2013, the proportion of sample use in newly initiated oral contraceptive therapy was 62.9 and 69.7 % for products that contain drospirenone and norethindrone, respectively, while sample provisions for products that contain levonorgestrel or norgestimate were too infrequent to produce reliable estimates (<3.0 %, Fig. 1d).

3.4 Additional Analyses

Table 2 contains additional detail for drugs with the most common sample use. In most instances, the provision of a sample at first use was accompanied by a prescription for the same drug. The only exception was ophthalmic moxifloxacin, for which dispensing of samples without a prescription for the same drug was more common. Similarly, when samples were dispensed during continued therapy, they were most often accompanied by a prescription for the same drug.

Except for the most frequently used drugs, data to evaluate the proportion of sample use by types of insurance benefits are limited. Among the most frequently used drugs, sample use tended to be somewhat less common among Medicaid recipients than among those with other types of insurance. In some instances, including new use of oral moxifloxacin and norethindrone, patients without insurance were more likely to receive a sample than patients with any type of insurance. Unfortunately, the use of most study drugs among patients without insurance benefits was infrequent, which meant we were unable to provide reliable estimates of sample provision rates in several instances.

Table 2 also presents the average number of sample days supplied per sample provision as reported by the physician. For chronically used drugs other than oral contraceptives, average sample duration for new use ranged from 13.4 days (dabigatran) to 22.8 days (exenatide). Average supply was similar for continued use, ranging from 14.7 days (dabigatran) to 25.3 days (exenatide). Average supply tended to be close to 30 days per sample provision when no prescription was issued and close to 15 days when a prescription for the same drug was issued during the same visit (data not shown). Among the drugs with short-term indications, the average supply for new use of oral and ophthalmic moxifloxacin was 4.8 and 5.8 days, respectively. Samples of oral contraceptives included the longest supply, led by products that contained levonorgestrel with average supplies of 85.6 and 85.1 days for new use and continued use, respectively (not shown).

4 Discussion

We conducted this study to explore the extent of sample use in various scenarios when sample use is likely to introduce bias in pharmacoepidemiology studies, including comparisons of newer vs. established drugs that are used for chronic and acute indications. Our analyses suggested that free samples are frequently used among initiators of brand-only drugs across several drug classes. In recent years, the use of samples was closely associated with a drug's first generic approval date, resulting in sample provision rates that differed widely between branded and generic drugs. Among brand-only drugs, samples were commonly provided when therapy was initiated and less commonly during continued use.

4.1 Comparison with Other Studies

Our findings differed from prior studies in some noteworthy aspects. Our estimate for sample provisions with new use of a brand-only statin (rosuvastatin 48.5 %) substantially exceeded the estimate of 13.4 % for branded statins by Li et al. [17]. However, while findings by Li et al. [17] relied on estimation of samples based on the distribution of laboratory values among those who fill a prescription in a pharmacy, our study estimated sample use as reported by healthcare providers, regardless of an eventual pharmacy claim. Thus, the studies differ in their denominators and a lower proportion of sample use would be expected among patients who eventually filled the prescription in the pharmacy compared with our physician office-based denominator.

Some of our findings corroborate findings from previous work. Not limiting to specific drugs, studies have found that approximately 50 % of Medicare beneficiaries obtained free drug samples [12, 15], but others have found lower rates [11]. Similar to other studies, we

found generally lower rates of sample use among Medicaid beneficiaries [4, 11] and higher rates among patients with private insurance, including health maintenance organizations and preferred provider organizations, or Medicare Part D benefits, especially for new use of branded drugs with chronic indications. Cost considerations may have resulted in frequent sample use of oral moxifloxacin in patients without insurance, where a single dispensing could provide a full course of therapy for an acute condition, similar to what was shown in a study among indigent patients [9].

4.2 Implications for Pharmacoepidemiology

The use of samples has important implications for descriptive and analytic pharmacoepidemiologic studies. In the case of drugs used for short-term indications, such as acute infections that are treated with moxifloxacin [18, 19], entire treatment episodes may be missed when researchers rely on drug exposure information from pharmacy claims data. For chronically used drugs, the majority of sample provisions were accompanied by prescriptions. However, we were unable to evaluate in our data whether or when patients ultimately filled their prescriptions, which is when a treatment episode would become apparent in pharmacy claims data. Sample use was present during continued therapy, which could have occurred either after patients filled a prescription in a pharmacy, or as a continuation of sequential sample use, possibly to ease financial burden. In the latter case, the duration of unobserved drug exposure would extend beyond the days of supply provided with the initial sample. Thus, sample use may completely mask the use of pharmacotherapy in acute conditions or may cause the appearance of delayed, interrupted, or discontinued pharmacotherapy in chronic conditions. Both effects can introduce bias in quality improvement studies by exacerbating findings of suboptimal adherence to treatment guidelines [1, 16].

Studies that compare event occurrences between initiators of newer, brand-only drugs with frequent sample use and established, generic drugs with infrequent sample use are at risk for bias due to exposure misclassification. While the impact of exposure misclassification may be minimal when the events of interest occur under a constant hazard [14], studies of events that tend to occur soon after drug initiation may be particularly biased when patients initiate therapy using samples and continue therapy with prescriptions dispensed in the pharmacy [13, 20]. In this case, early events during high-risk periods would not be attributed to the drug of interest, resulting in attenuated estimates of incidence rates among the exposed and biased incidence rate ratios. Gamble et al. [21] have shown that delayed ascertainment of exposure can even reverse observed associations. Examples for adverse events that tend to occur early after drug initiation include myopathy with statins [22], serious anaphylactic reactions with antibiotics [19], and venous thromboembolism with certain oral contraceptives [23]. Due to very high sample dispensing rates with both new and continued use of some but not all oral contraceptives, the latter example is especially prone to bias.

Additionally, sample recipients whose exposure is only ascertained after they eventually fill a prescription for the same drug in a pharmacy are mischaracterized as incident users of the drug at the time of their first pharmacy claim [24]. With that, depletion of susceptibles becomes a concern, because continuing users have demonstrated that they can tolerate or did

not experience early side effects of the drug and may therefore be a lower risk for additional adverse events [25]. This differential patient selection would potentially result in biased effect estimates, to the advantage of the drug with higher rates of sample use.

4.3 Recommendations

Researchers should attempt to quantify the impact of exposure misclassification in their studies. However, biases resulting from the inability to establish new use are especially difficult to address [13]. Nevertheless, we strongly encourage researchers to use sensitivity analyses in their own studies, for instance by analyzing event rates during periods that precede apparent treatment initiation as observed from pharmacy claims data. Such an approach may inform about issues related to early events, but it would not address depletion of susceptibles, because those who experience an event of interest during sample use may not fill a prescription in a pharmacy and would not be categorized as users of the drug.

Although we observed some differences in rates of sample use by type of insurance benefits, these differences were often modest and not consistent between different drugs. Therefore, when concerns exist about exposure misclassification as a consequence of sample use, the choice of a different, US-based data source may not eliminate these concerns. Because sampling is predominantly practiced in the USA [2], researchers may consider the use of international databases, from countries where drug samples are not provided in physician offices.

4.4 Limitations

The first limitation is related to the cross-sectional nature of our data, which does not allow for the assessment of the total duration of sample use for individual patients. While we were able to establish the presence of sample use during new and continuing therapy, future studies should employ methodology that can measure the total duration of sample use in individual patients to inform sensitivity analyses in pharmacoepidemiologic studies. The second limitation concerns the data origin, namely physician surveys. We are not aware of existing validation studies that support the accuracy and completeness of the provided information on sample dispensing in physician offices. Inaccuracy could arise when samples are provided in a physician's office by individuals who are not involved in filling out the survey, combined with insufficient internal record keeping. In addition, physicians who participate in the survey may differ from non-participating physicians in their frequency of encounters with sales representatives and in their attitudes towards accepting and providing prescription drug samples. Similarly, we restricted our sample to include only office-based physicians. Rates of sample provision observed in our study may not be readily applicable to hospital or institutional settings. Nevertheless, face validity is apparent in the general agreement of trends of sample use in recent years with the introduction of generic drugs, with the exception of pioglitazone, where sample use started to decline around the time of emerging safety concerns, amid a decline in overall use of pioglitazone [26–28]. Finally, the survey was large enough to provide reliable, nationally projected estimates for sample use among commonly used drugs. However, due to sample size limitations, we were unable to study predictors for sample use, including patient age, race, setting of care, physician

specialty and years in practice, and geographic region. We refer to other studies for predictors of sample use [4, 11, 12, 29].

4.5 Strengths

Strengths of our study include that it provides nationally representative estimates of sample use that are based on direct assessments from the point of sample provision and that it does not rely on inferences made using indirect methodology. Furthermore, we stratified our data by therapeutic class, generic availability, new versus continued use, and type of insurance to provide information most relevant to various pharmacoepidemiologic study scenarios.

5 Conclusions

This study found substantial use of samples during newly initiated therapy with patented prescription drugs as reported in US office-based physician survey data. We described mechanisms whereby differential use of samples between brand-only and generically available drugs can lead to biased estimates of adverse event rates, especially when the risk for adverse events is elevated early after drug initiation. Researchers should make use of existing methodology to quantify bias associated with exposure misclassification and develop new methodology to account for reduced ability to establish incident drug use.

Acknowledgments

Funding No sources of funding were used to assist in the preparation of this study.

References

1. Choudhry NK, Shrank WH. Four-dollar generics–increased accessibility, impaired quality assurance. N Engl J Med. 2010; 363(20):1885–7. [PubMed: 21067379]
2. Chimonas S, Kassirer JP. No more free drug samples? PLoS Med. 2009; 6(5):e1000074. [PubMed: 19434227]
3. Vincent WR, Wiesner AM, Steinke DT. “Free” prescription drug samples are not free. Am J Public Health. 2008; 98(8):1348–9. [PubMed: 18556595]
4. Alexander GC, Zhang J, Basu A. Characteristics of patients receiving pharmaceutical samples and association between sample receipt and out-of-pocket prescription costs. Med Care. 2008; 46(4): 394–402. [PubMed: 18362819]
5. Chew LD, O'Young TS, Hazlet TK, Bradley KA, Maynard C, Lessler DS. A physician survey of the effect of drug sample availability on physicians' behavior. J Gen Intern Med. 2000; 15(7):478–83. [PubMed: 10940134]
6. Hartung DM, Evans D, Haxby DG, Kraemer DF, Andeen G, Fagnan LJ. Effect of drug sample removal on prescribing in a family practice clinic. Ann Fam Med. 2010; 8(5):402–9. [PubMed: 20843881]
7. Miller DP, Mansfield RJ, Woods JB, Wofford JL, Moran WP. The impact of drug samples on prescribing to the uninsured. South Med J. 2008; 101(9):888–93. [PubMed: 18708971]
8. Westfall JM, McCabe J, Nicholas RA. Personal use of drug samples by physicians and office staff. JAMA. 1997; 278(2):141–3. [PubMed: 9214530]
9. Mabins MN, Emptage RE, Giannamore MR, Hall LE. Drug sample provision and its effect on continuous drug therapy in an indigent care setting. J Am Pharm Assoc. 2003; 47(3):366–72.
10. Hurley MP, Stafford RS, Lane AT. Characterizing the relationship between free drug samples and prescription patterns for acne vulgaris and rosacea. JAMA Dermatol. 2014; 150(5):487–93. [PubMed: 24740450]

11. Cutrona SL, Woolhandler S, Lasser KE, Bor DH, McCormick D, Himmelstein DU. Characteristics of recipients of free prescription drug samples: a nationally representative analysis. Am J Public Health. 2008; 98(2):284–9. [PubMed: 18172135]
12. Tjia J, Briesacher BA, Soumerai SB, Pierre-Jacques M, Zhang F, Ross-Degnan D, et al. Medicare beneficiaries and free prescription drug samples: a national survey. J Gen Intern Med. 2008; 23(6): 709–14. [PubMed: 18365289]
13. Johnsson Funk M, Landi NL. Misclassification in administrative claims data: quantifying the impact of treatment effect estimates. Curr Epidemiol Rep. 2014; 2014(1):175–85.
14. Jacobus S, Schneeweiss S, Chan KA. Exposure misclassification as a result of free sample drug utilization in automated claims databases and its effect on a pharmacoepidemiology study of selective COX-2 inhibitors. Pharmacoepidemiol Drug Saf. 2004; 13(10):695–702. [PubMed: 15386727]
15. Gellad WF, Huskamp HA, Li A, Zhang Y, Safran DG, Donohue JM. Use of prescription drug samples and patient assistance programs, and the role of doctor-patient communication. J Gen Intern Med. 2011; 26(12):1458–64. [PubMed: 21751052]
16. Lauffenburger JC, Balasubramanian A, Farley JF, Critchlow CW, O'Malley CD, Roth MT, et al. Completeness of prescription information in US commercial claims databases. Pharmacoepidemiol Drug Saf. 2013; 22(8):899–906. [PubMed: 23696101]
17. Li X, Sturmer T, Brookhart MA. Evidence of sample use among new users of statins: implications for pharmacoepidemiology. Med Care. 2014; 52(9):773–80. [PubMed: 24984210]
18. [Accessed 21 Nov 2014] Vigamox label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021598s017lbl.pdf
19. [Accessed 20 Nov 2014] Avelox label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021085s057,021277s054lbl.pdf
20. Guess HA. Behavior of the exposure odds ratio in a case-control study when the hazard function is not constant over time. J Clin Epidemiol. 1989; 42(12):1179–84. [PubMed: 2585009]
21. Gamble JM, McAlister FA, Johnson JA, Eurich DT. Quantifying the impact of drug exposure misclassification due to restrictive drug coverage in administrative databases: a simulation cohort study. Value Health. 2012; 15(1):191–7. [PubMed: 22264988]
22. [Accessed 20 Nov 2014] Zocor label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019766s091lbl.pdf
23. [Accessed 20 Nov 2014] Yaz label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021676s012lbl.pdf
24. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003; 158(9):915–20. [PubMed: 14585769]
25. Moride Y, Abenhaim L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. J Clin Epidemiol. 1994; 47(7):731–7. [PubMed: 7722586]
26. Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP Jr, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care. 2011; 34(4):916–22. [PubMed: 21447663]
27. Food and Drug Administration. [Accessed 21 Nov 2014] Drug safety communication: ongoing safety review of actos (pioglitazone) and potential increased risk of bladder cancer after two years exposure. Sep 17. 2010 http://www.fda.gov/Drugs/DrugSafety/ucm226214.htm
28. Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of antidiabetic drugs in the US, 2003–2012. Diabetes Care. 2014; 37(5):1367–74. [PubMed: 24623020]
29. Cutrona SL, Woolhandler S, Lasser KE, Bor DH, Himmelstein DU, Shrank WH, et al. Free drug samples in the United States: characteristics of pediatric recipients and safety concerns. Pediatrics. 2008; 122(4):736–42. [PubMed: 18829796]

Key Points

Drug samples dispensed in physician offices can lead to exposure misclassification in pharmacoepidemiologic studies that rely on pharmacy claims data.

The provision of drug samples in US physician offices is common at the beginning of therapy with branded drugs and uncommon with most generic drugs. Sample use is still present during continued therapy, albeit at lower levels.

Differential sample use can introduce bias in pharmacoepidemiologic studies, in particular, when brand-only drugs are compared with generically available drugs, and the risk for the outcome of interest is highest shortly after initiation of therapy.

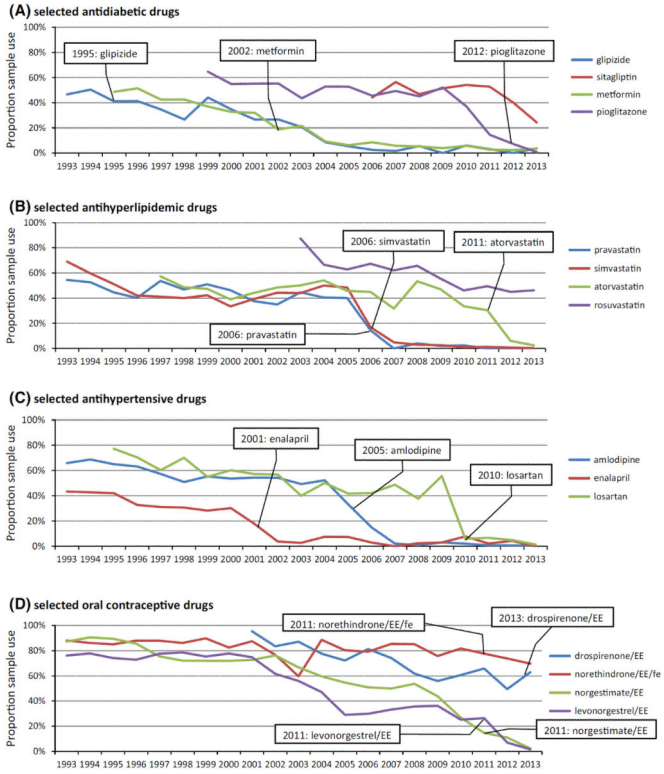

Fig. 1.

Proportion of sample use among newly initiated therapy, 1993–2013. **a** selected antidiabetic drugs; **b** selected antihyperlipidemic drugs; **c** selected antihypertensive drugs; **d** selected oral contraceptive drugs. *Boxes* indicate approval year of first generic version. Data source: Encuity Research, LLC, TreatmentAnswers™ Audit. Extracted June 2014

Table 1

Proportion of sample use for newer and established drugs in the USA, 2009–2013

	Approval	Generic approval	New use, sample any (%)[a]	Continued use, sample any (%)[a]
Antidiabetic drugs				
Sitagliptin	2006	–	44.7	17.0
Exenatide	2005	–	38.1	9.8
Pioglitazone	1999	2012	28.5	12.4
Metformin	1995	2002	3.6	1.2
Glipizide	1984	1995	<3.0[b]	<3.0[b]
Antihyperlipidemic drugs				
Rosuvastatin	2003	–	48.5	23.9
Atorvastatin	1996	2011	22.9	9.1
Simvastatin	1991	2006	1.2	1.1
Pravastatin	1991	2006	<3.0[b]	<3.0[b]
Antihypertensive drugs				
Losartan	1995	2010	11.8	2.6
Amlodipine	1992	2005	1.3	0.9
Enalapril	1985	2001	>3.0[b]	<3.0[b]
Anticoagulants				
Dabigatran	2010	–	43.5	22.7
Warfarin	1954	1997	<3.0[b]	<3.0[b]
Antibiotics, oral				
Moxifloxacin	1999	2014	24.3	>3.0[b]
Levofloxacin	1996	2011	8.1	>3.0[b]
Ciprofloxacin	1987	2004	3.7	5.3
Antibiotics, ophthalmic				
Moxifloxacin	2003	–	14.0	>3.0[b]
Levofloxacin	2000	2011	40.1	>3.0[b]
Ciprofloxacin	1990	2004	7.4	>3.0[b]
Drugs for ADHD				
Atomoxetine	2002	–	27.7	14.4
Methylphenidate	1955	1997	<3.0[b]	0.7
Oral contraceptives containing				
Drospirenone/EE	2001	2013	59.4	38.1
Norgestimate/EE	1992	2011	20.3	11.5
Levonorgestrel/EE	1982	2011	20.9	12.4
Norethindrone/EE/fe	1976	2011	75.3	55.8

Data source: Encuity Research, LLC, TreatmentAnswers™ Audit. Extracted June 2014

ADHD attention-deflcit/hyperactivity disorder. *EE* ethinyl estradiol, *fe* ferrous fumarate

[a] Proportion of visits during which a sample was provided among visits with issued prescription and/or sample of drug of interest

[b] Based on fewer than 100,000 projected counts

Table 2

Proportion of sample use for selected study drugs with the highest projected sample use during the last 5 calendar years of market exclusivity

	Rosuvastatin (2009–2013)		Sitagliptin (2009–2013)		Exenatide (2009–2013)		Losartan (2005–2009)		Dabigatran (2010–2013)	
	New	Cont	New	Cont	New	Cont	New	Cont	New	Cont
Visits[a] (*n* × 1000)	10,937	16,779	3645	4764	905	1077	3064	7471	1217	944
Sample only	8.6	4.7	9.9	3.7	>3.0[b]	>3.0[b]	12.8	5.8	15.0	10.5
Sample + Rx	39.9	19.3	34.8	13.3	29.1	>3.0[b]	32.2	12.0	28.5	12.2
Sample any	48.5	23.9	44.7	17.0	38.1	9.8	45.0	17.8	43.5	22.7
Sample days, weighted average	17.8	18.9	17.2	24.5	22.8	25.3	18.6	19.7	13.4	14.7
Insurance type, % sample any										
Private	45.3	20.8	31.1	23.1	>3.0[b]	>3.0[b]	56.2	9.1	>3.0[b]	>3.0[b]
HMO	50.7	24.0	59.2	>3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]	15.4	>3.0[b]	>3.0[b]
PPO	61.7	24.6	48.9	13.0	>3.0[b]	>3.0[b]	44.2	>3.0[b]	>3.0[b]	<3.0[b]
Medicare Part D	41.3	22.6	53.4	15.5	>3.0[b]	>3.0[b]	58.8	31.7	51.0	23.2
Medicaid	27.2	26.8	30.0	>3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]	<3.0[b]
No insurance	>3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]	<3.0[b]	<3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]

	Moxifloxacin, oral (2009–2013)		Moxifloxacin, ophthalmic (2009–2013)		Atomoxetine (2009–2013)		Drospirenone/EE (2008–2012)		Norethindrone/EE/fe (2006–2010)	
	New	Cont	New	Cont	New	Cont	New	Cont	New	Cont
Visits[a] (*n* × 1000)	12,117	255	11,989	369	1048	2139	6634	12,145	7288	6710
Sample only	10.0	>3.0[b]	8.2	>3.0[b]	13.4	>3.0[b]	16.6	4.7	24.7	17.6
Sample + Rx	14.4	>3.0[b]	5.8	<3.0[b]	14.3	10.5	43.3	35.9	56.8	45.1
Sample any	24.3	>3.0[b]	14.0	>3.0[b]	27.7	14.4	59.9	40.6	81.5	62.7
Sample days, weighted average	4.8	4.9	5.8	6.8	21.1	15.5	44.6	41.2	47.1	41.9
Insurance type, % sample any										
Private	15.2	>3.0[b]	17.9	>3.0[b]	40.0	25.9	61.5	42.7	87.4	73.1

	Moxifloxacin, oral (2009–2013)		Moxifloxacin, ophthalmic (2009–2013)		Atomoxetine (2009–2013)		Drospirenone/EE (2008–2012)		Norethindrone/EE/fe (2006–2010)	
	New	Cont	New	Cont	New	Cont	New	Cont	New	Cont
HMO	17.0	>3.0[b]	13.7	>3.0[b]	>3.0[b]	>3.0[b]	56.0	43.8	79.5	57.4
PPO	32.9	>3.0[b]	13.8	>3.0[b]	>3.0[b]	>3.0[b]	62.0	38.4	80.9	59.5
Medicare part D	35.6	>3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]	<3.0[b]	>3.0[b]	>3.0[b]
Medicaid	14.2	>3.0[b]	10.0	<3.0[b]	>3.0[b]	>3.0[b]	63.1	>3.0[b]	74.3	68.9
No insurance	55.5	>3.0[b]	11.9	>3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]	>3.0[b]	85.4	>3.0[b]

Data are presented as % unless otherwise indicated. Sample only refers to provision of a sample without accompanying prescription, sample + Rx refers to the provision of a sample together with a prescription for the same drug, and sample any is the sum of sample only and sample + Rx. Data Source: Encuity Research, LLC, TreatmentAnswers™ Audit. Extracted June 2014

Cont continued use, *EE* ethinyl estradiol, *HMO* health maintenance organization, *PPO* preferred provider organization, *Rx* prescription

[a] Visits during which prescription was issued and/or sample was provided for drug of interest

[b] Based on fewer than 100,000 projected counts