ORIGINAL RESEARCH

Sample Closet Medications Are Neither Novel Nor Useful

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Background: **Many physicians dispense drug samples in their offices, but this practice may not benefit patients. We analyzed the novelty and usefulness of the medications most commonly found in sample closets in primary care practices.**

Methods: **In this cross-sectional study, we inventoried 10 sample closets from internal medicine and family practice offices in the Phoenix metropolitan area. We analyzed 23 medications found in 7 or more closets. To assess novelty, we determined whether the sample medication had a new mechanism of action, a generic version with the same mechanism of action on the market, and a generic medication for the same indication on the market. To assess usefulness, we determined whether the sample medication improved patient-oriented outcomes, safety, and tolerability. We noted the cost of a 1-month supply for a typical starting dose.**

Results: **Ninety-six percent (n = 22) of sample closet medications had a generic medication for the same indication and 74% (n = 17) had a generic medication with the same mechanism available on the market. Only 3 medications (13%) had evidence of superior patient-oriented outcomes when compared with other medications for the same indication. Six medications (26%) demonstrated superior safety or tolerability. Only one medication (4%) was recommended as a first-line therapy in an evidence-based guideline. The mean cost for a 1-month supply of a typical starting dose was $178.**

Conclusions: **Sample closet medications have limited novelty and usefulness and are often expensive. The widespread use of sample medications should be reexamined. (J Am Board Fam Med 2013;26: 380–387.)**

Keywords: **Health Policy, Practice Management, Primary Health Care, Quality of Health Care**

Sample medications are commonly distributed in physician offices in the United States. In a 2009 survey, 80% of cardiologists, 70% of family physicians, and 67% of internists reported receiving drug samples.[1] Sample medications are dispensed in 20% of office encounters,[2] and 12% of the US population receives drug samples annually.[3] In 2004, the pharmaceutical industry spent $16.4 billion on the provision of sample drugs in the United States.[3] Advocates argue that sample medications are convenient, provide a source of medication to patients in need, allow physicians to evaluate the effectiveness and tolerability of a medication, and allow prompt treatment.[4] However, substantial evidence indicates that the use of sample medications may not benefit patients.

Physicians and office staff often use sample drugs for themselves or their families.[5] Contrary to the commonly held belief that samples are used for those patients most in need, samples are used more frequently by the wealthy and insured. In a recent study, 82% of patients receiving samples were insured the entire year, and 72% of patients receiving samples had an income at least 200% above the federal poverty line.[3]

This article was externally peer reviewed.

Submitted 7 December 2012; revised 18 February 2013; accepted 22 February 2013.

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Funding: none.

Prior presentation: Presented at a research forum at the Society of Teachers of Family Medicine Annual Spring Conference, April 27, 2012, Seattle, WA.

Conflict of interest: SRB is a commentator for Primary Care Medical Abstracts and an associate editor for Essential Evidence. GWS has served as a consultant to Anvita Health.

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The use of sample medications that bypass office-based electronic medical records increases the risk of unintended drug interactions. A recent survey showed that physicians are concerned that dispensing of office samples bypasses counseling by pharmacists, which can help maximize therapeutic outcomes.[6] Drug samples also affect physician prescribing practices and affect the cost of drugs for patients. Physicians are more likely to prescribe drugs that differ from their preferred drug choice and deviate from the usual standards of care.[4,7,8] Although patients may perceive a financial benefit from "free" sample drugs, because of subsequent prescription copayment expenses their out of pocket cost is actually higher.[9]

Drug samples are "almost never time worn and well-tested drugs … and usually comprise the newest drugs on the market."[10] Many new drugs on the market are "me too" drugs, a new drug within an existing class of medications that offers minimal additional therapeutic benefit.[11] In addition, the long-term safety of newly approved drugs is often unknown.[12,13]

Newly approved drugs, including those most likely to be found in samples closets, are often not novel or useful.[9] For example, in one analysis of new drugs approved by the US Food and Drug Administration (FDA) in 2008, not a single new drug was both novel and relevant to primary care.[11] Many newly approved drugs are heavily marketed as samples.

To our knowledge, no prior study has inventoried sample closets and examined the novelty and usefulness of their contents. In this study, we analyze the medications most commonly found in sample closets to assess their novelty and usefulness in primary care practice.

Methods

We inventoried the drug sample closets of 10 primary care offices in the Phoenix metropolitan area. We selected a convenience sample of clinics that teach the University of Arizona College of Medicine's Longitudinal Clinical Experience curriculum and that were known to have sample closets. We inventoried 7 family medicine and 3 internal medicine offices. Six were group practices and 4 were solo practices. Five were affiliated with a hospital and 5 were private practices. We obtained signed informed consent from each practice site. The University of Arizona College of Medicine institutional review board approved the study. We analyzed each closet on one day between November 2009 and June 2010 and for each sample medication recorded the drug name, quantity, expiration date, and dosage. We selected drugs for study if they were present in at least 7 of the 10 practice sites.

We independently assessed the novelty and usefulness of the medications, resolving differences by consensus. We established novelty by the response to 3 questions: (1) Is the medication the first in a new drug class or does it work by a novel pharmacologic mechanism? (2) Is there a generic medication with the same pharmacologic mechanism already on the market? and (3) Is there a generic medication for the same indication already on the market? Pharmacologic mechanism is defined as the mechanism by which the drug is effective; for example, rosuvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. We defined usefulness based on the answers to 4 core questions: (1) Do published randomized control trials (RCTs) or systematic reviews with patient-oriented outcomes demonstrate that the medication is superior to medications for the same indication already on the market? (2) Do comparative efficacy RCTs or systematic reviews demonstrate increased safety or tolerability compared with medications for the same condition or indication already on the market? and (3) Is the medication recommended as a first-line agent in an evidence-based guideline?

We documented the year of FDA approval, indication, and drug mechanism. For the usefulness questions, we searched MEDLINE with limits on RCTs and systematic reviews, the National Guideline Clearinghouse (www.guideline.gov), and the clinical reference tools DynaMed and Micromedex. We estimated the average wholesale price for a 1-month starting dose of each medication based on Price Alert, Drugstore.com, and the Pharmacist's Letter.

Results

The 10 sample closets contained 12,581 individual sample packets/boxes of medication, with a mean of 1258 (standard deviation, 785; range, 83–2850) per closet. The 10 closets had a mean of 123 different medications (standard deviation, 65; range, 6–241). Twenty-seven individual medications were common to at least 7 of the 10 sample closets. We

Table 1. Characteristics of the Medications Most Commonly Found in Sample Closets and Their Costs

Trade Name	Generic Name	Date Initially Approved by FDA	Sites Containing Sample (n)	Indications	Most Common Initial Dose	AWP*
Bystolic	Nebivolol	2007	9	Hypertension	5 mg daily	$68/30 tabs
Crestor	Rosuvastatin	2003	9	Hyperlipidemia	10 mg daily	$157/30 tabs
Januvia	Sitagliptin	2006	9	Type 2 diabetes	100 mg daily	$244/30 tabs
Micardis	Telmisartan	1998	9	Hypertension	40 mg daily	$124/30 tabs
Toviaz	Fesoterodine	2008	9	Overactive bladder	4 mg daily	$159/30 tabs
Avodart	Dutasteride	2001	8	Benign prostate hyperplasia	0.5 mg daily	$129/30 tabs
Cymbalta	Duloxetine	2004	8	Depression, anxiety	60 mg daily	$183/30 caps
Diovan	Valsartan	2001	8	Hypertension	80 mg daily	$97/30 tabs
Lipitor	Atorvastatin	1996	8	Hyperlipidemia	20 mg daily	$183/30 tabs
Lovaza	Omega-3-acid ethyl esters	2004	8	Hypertriglyceridemia	4 g daily	$190/120 1-g caps
Pristiq	Desvenlafaxine	2008	8	Depression	50 mg daily	$153/30 tabs
Seroquel	Quetiapine	1997	8	Schizophrenia, bipolar disorder	200 mg BID	$749/60 tabs
Actos	Pioglitazone	1999	7	Type 2 diabetes	30 mg daily	
Amitiza	Lubiprostone	2006	7	Chronic idiopathic constipation	24 μg BID	$272/60 caps
Celebrex	Celecoxib	1998	7	Joint pain	100 mg BID	$176/60 caps
Enablex	Darifenacin	2004	7	Overactive bladder	7.5 mg daily	$167/30 tabs
Levitra	Vardenafil	2003	7	Erectile dysfunction	10 mg	$21/tab
Maxalt	Rizatriptan	1998	7	Migraine headache	5 mg	$32/tab
Savella	Milnacipran	2009	7	Fibromyalgia	50 mg BID	$146/60 tabs
Spiriva	Tiotropium	2004	7	COPD	1 capsule (18 μg) daily	$289/30 caps
Synthroid	Levothyroxine	2002	7	Hypothyroidism	100 μg daily	$21/30 tabs
Trilipix	Fenofibric acid	2008	7	Hyperlipidemia, hypertriglyceridemia	45 mg daily	$54/30 caps
Vytorin	Ezetimibe and simvastatin	2004	7	Hyperlipidemia	10/20 mg daily	$148/30 tabs

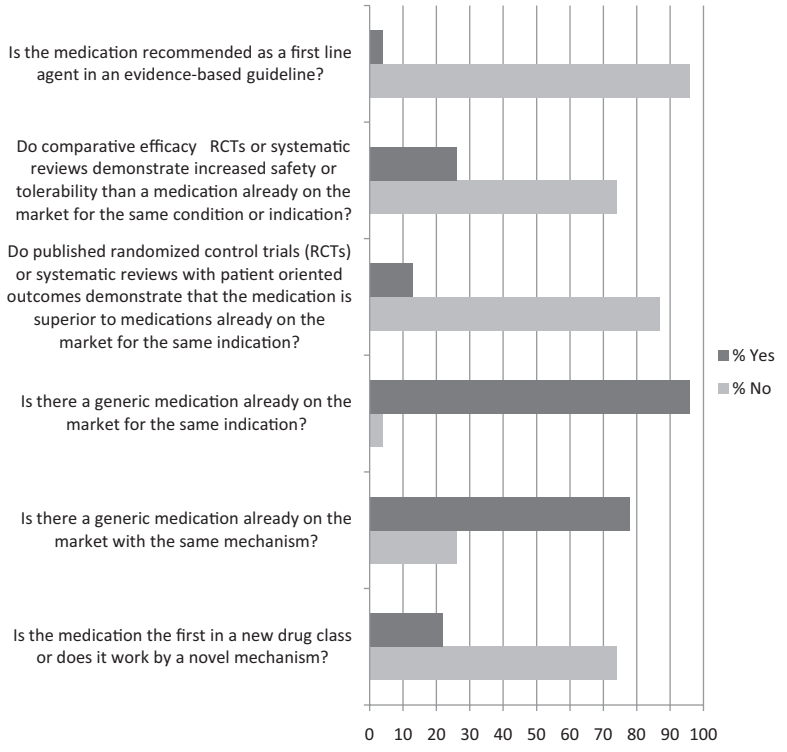
*Cost of a 30-day supply of the most commonly used initial dose of the medication.
AWP, average wholesale price; Cap, capsule; COPD, chronic obstructive pulmonary disease; FDA, US Food and Drug Administration; tab, tablet.

excluded 4 of these 27 medications from the study because they were combination drugs that fell into 2 separate medication classes (for example, Exforge, found in 7 sample closets, is a combination of amlodipine and valsartan). We included the medication that combines ezetimibe and simvastatin and analyzed it based on the more novel component because ezetimibe was the only novel drug in a combination medication. We also excluded nonprescription drugs (n = 18), such as over-the-counter medications or herbal remedies, from the analysis.

We analyzed the remaining 23 medications that we found in 7 or more of the inventoried sample closets. Five sample types were present in 9 closets, 7 sample types were present in 8 closets, and 11 sample types were present in 7 closets. Table 1 lists those medications found in at least 7 of the 10 closets and the clinical indications and average monthly cost for the commonly used starting dose of each.

Figure 1 displays the proportion of the 23 medications that had novel or useful attributes on the basis of our 6 prespecified questions. Of these drugs, 78% (n = 18) were neither the first in a new drug class nor the first to work by a new mechanism. For 74% (n = 17) of the drugs, a generic medication with the same mechanism was already on the market. In nearly all cases (96%; n = 22) a generic medication for the same indication was already on the market. For 87% (n = 20) of drugs, no RCTs or systemic reviews with patient-oriented outcomes demonstrated superiority to medications

Figure 1. Percentage of yes and no answers regarding novelty and usefulness of most commonly found sample drugs. RCT, randomized control trials.



for the same indication that were already on the market. For 74% (n = 17) of the medications, no published RCTs or systemic reviews demonstrated superior safety or tolerability. One (4%) of the medications is recommended as first-line therapy in an evidence-based guideline. Table 2 shows the guideline used to evaluate each medication.

The average wholesale price for 1 month of the most commonly used starting dose for each analyzed drug is shown in Table 1. One drug, atorvastatin, is now available as a generic; however, the average wholesale price is listed for the branded drug since the branded drug was found in sample closets. The mean cost of a 1 month supply of the most commonly used starting dose for each of the 23 analyzed drugs was $178, with a median of $158, minimum of $21, and maximum of $749. In 20 of 23 instances, a generic alternative was available at a commonly used pharmacy for $4 per month.[28]

Discussion

In this study, we found that the medications most commonly found in drug sample closets are rarely novel or useful and are expensive. Only 5 of the 23 medications are the first in a new class of medications. The remainder of the medications are "me too" drugs, that is, medications in the same drug class as an existing medication that offer little additional benefit.[29] For example, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors rosuvastatin and atorvastatin were found in 9 and 8 sample closets, respectively. These drugs are among 8 "statin" drugs on the market, including 3 that are currently available as generics.[29] All medications except one, vardenafil, have a generic drug for the same indication available on the market.

In addition, commonly sampled medications are often not useful. To be useful, a medication should be safer or more effective than existing medications as indicated in comparative effectiveness studies. Evidence for greater efficacy would come from patient-oriented outcomes such as morbidity, mortality, and quality of life rather than surrogate, or proxy, markers. In our study, for 20 of the 23 sample closet medications, no studies demonstrated superior patient-oriented outcomes. This is not surprising. The FDA commonly approves drugs based on improvements in a surrogate marker (eg, blood pressure). Although studies of clinically meaningful outcome measures may exist, they commonly compare the

Table 2. Medications Most Commonly Found in Sample Closets and the Relevant Guideline to Evaluate Usefulness

Trade Name	Generic name	Relevant Guideline
Synthroid	Levothyroxine	AACE 2002[14]
Maxalt	Rizatriptan	AAFP/ACP-ASIM 2002[15]
Levitra	Vardenafil	ACP 2010[16]
Celebrex	Celecoxib	ACR 2012[17]
Januvia	Sitagliptin	ADA 2012[18]
Actos	Pioglitazone	ADA 2012[18]
Cymbalta	Duloxetine	APA 2010[19]
Pristiq	Desvenlafaxine	APA 2010[19]
Amitiza	Lubiprostone	ASCRS 2007[20]
Lovaza	Omega-3-acid ethyl esters	ATP III 2004[21]
Crestor	Rosuvastatin	ATP III 2004[21]
Lipitor	Atorvastatin	ATP III 2004[21]
Trilipix	Fenofibric Acid	ATP III 2004[21]
Vytorin	Ezetimibe and simvastatin	ATP III 2004[21]
Avodart	Dutasteride	AUA[22]
Savella	Milnacipran	EULAR 2008[23]
Spiriva	Tiotropium	GOLD 2010[24]
Bystolic	Nebivolol	JNC VII[25]
Micardis	Telmisartan	JNC VII[25]
Diovan	Valsartan	JNC VII[25]
Toviaz	Fesoterodine	NICE 2006[26]
Enablex	Darifenacin	NICE 2006[26]
Seroquel	Quetiapine	NICE 2006[27]

AACE, American Association of Clinical Endocrinologists; AAFP, American Academy of Family Physicians; ACP-ASIM, American College of Physicians-American Society of Internal Medicine; ADA, American Diabetes Association; ACR, American College of Rheumatism; APA, American Psychiatric Association; ASCRS, American Society of Colon and Rectal Surgeons; ATP, Adult Treatment Panel; AUA, American Urologic Association; EULAR, European League Against Rheumatism; GOLD, Global Initiative for Chronic Obstructive Lung Disease; JNC, Joint National Committee; NICE, National Institute for Clinical Excellence (UK).

drug only to placebo rather than to existing medications.[30]

Superior safety or tolerability data existed for only 26% of the sample closet drugs. Even this figure may actually overstate the incremental benefit of the sampled medications. Often, the incremental improvement in tolerability or safety existed only in a limited number of industry-funded studies. In no instance did the evidence base indicate that a sample closet medication was safer or better tolerated than every available alternative medication. If a new medication improves neither patient-oriented outcomes nor tolerability, its usefulness is limited.

The medications found most commonly in sample closets are rarely first-line agents according to published guidelines. Clinical practice guidelines are "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[31] In each instance, we identified a guideline that pertained to the indication for the particular sample closet medication. For example, the Joint National Committee 7 guidelines for the evaluation and treatment of hypertension[25] address the 3 medications approved for hypertension (nebivolol, telmisartan, and valsartan) and the National Institute for Clinical Excellence overactive bladder guideline[26] discusses the 2 medications approved for that indication (fesoterodine and darifenacin). Several medications are listed among guideline options, such as rizatriptan for migraine, but often a generic is also listed as an option in the guidelines. We determined that one medication, Synthroid (levothyroxine), is a first-line treatment for the approved condition based on a national guideline. However, its generic version, levothyroxine, is equivalent[32] and less expensive.

When compared with generic medications, sample closet medications are expensive: the cost was as high as $749 per month, while the mean was $178 per month. Many applicable generics are available at low cost—as low as $4 per month in selected "big box" and retail pharmacies. After a supply of "free" samples is depleted, a patient often will continue the same medication at a higher cost to both the patient and the health care system.[9] In addition to the patient-level cost, the use of expensive medications costs the US health system billions of dollars annually.[10] For example, the use of brand-name cholesterol-lowering medications, instead of generics, costs the US health care system $5.8 billion dollars annually.[33] In addition, nonadherence is common when the cost to the patient is high; this has the potential to increase morbidity.[34–36]

There are several limitations to our study. First, it is a small cross-sectional study in one metropolitan area over one period of time. It is possible that the closets we inventoried during this time frame are not representative of sample closets nationwide. Further study should include inventories of sample closets across a greater variety of practices nation-

wide in both urban and rural as well as academic and private practice settings. In addition, it is not known whether these samples are representative of the entire year. The wide standard deviation of the number of drugs in each sample closet indicates that the inventory of more closets could be useful. Additional and larger studies could lead to a better understanding of the novelty and usefulness of sample closet medications and improve generalizability. Second, the 6 questions we selected to analyze the novelty and usefulness of the sample medications could be an oversimplification. Estimates of novelty and usefulness based on our questions may have been biased in unforeseen ways. In particular, we had thoroughly reviewed the literature and hypothesized that samples were not likely to be novel or useful. We included a nationally recognized expert on novelty and usefulness of new medications (GWS) in our author group to minimize this observer bias. Finally, while we performed a careful search of the literature to identify relevant practice guidelines, it is possible that we have overlooked guidelines that would have changed some of our conclusions.

On the basis of compelling evidence that sample medications are often no safer or more effective than less expensive alternatives, many have called for the cessation of the distribution of samples.[10,37–40] Indeed, many physicians already have chosen to close their sample closets; the number of physicians accepting samples has decreased from 78% in 2004 to 64% in 2009.[1] Many academic medical centers and residency training programs prohibit the use of samples.[10,41]

Sample closets also require considerable maintenance and are subject to increasingly complex regulatory requirements. A physician or member of the office staff must organize the samples, dispose of expired medications, and accurately track sample distribution.[42,43] Drugs in sample closets are often expired, leading to a potential for decreased therapeutic efficacy and an estimated waste of $2 billion annually.[44]

What are the alternatives to a sample closet? Physicians should consider nonpharmacologic treatment strategies when possible. When a medication is appropriate, physicians should consult both local institutional formularies and evidence-based guidelines that emphasize low-cost generics.[36] Erickson and Cullison[38] have proposed a low-cost, physician-sponsored closet of generic medications for patients in need. "Counter detailing," evidence-based prescribing advice in an office setting by nonconflicted local and national experts, provides an alternative to pharmaceutical detailing.[45–47]

There are some instances where thoughtful, evidence-based use of medications that can be accessed immediately may be considered in select populations, such as the underserved. In some cases, as with inhalers for asthma, there are no drugs available on the low-cost generic list. Alternatives to sample closet medications need to be considered carefully for patients who may not have adequate access to medication. Even in uninsured populations, samples should be used with caution because they may lead to worse outcomes in select conditions.[48] The availability and usefulness of sample closet medications among the underserved deserves further study.

Sample closet medications most often are no safer and are neither novel nor more effective than existing generic alternatives. Sample closet medications also increase the cost to both the patient and society. Guideline-based prescribing increases the use of medications that have a longer track record of safety and efficacy. The time has come to reexamine the use of sample closets.

The authors thank Michelle Agresti, PharmD, Clinical Pharmacist, Beth Israel Deaconess Physician Organization, who consulted on drug prices.

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