

What's in your sample closet? A cross-sectional study to quantify the number of expired samples and to evaluate novelty and usefulness of sample closet medications

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Presentations and Publications

This research was presented in a research forum: Evans KL, Brown SR, Smetana GW. Sample closet medications: Expensive, no more effective than existing medications, and often expired. Research forum at the Society of Teachers of Family Medicine Annual Spring Conference. Seattle, WA. April 27, 2012.

Part of this research has been published in a peer-reviewed publication: Evans KL, Brown SR. Many sample closet medications are expired. *J Am Board Fam Med* 2012;25(3):394-5.

Abstract.

Background

Many physicians dispense drug samples in their offices. In general, evidence suggests that drug samples provide minimal benefit to patients.

Objective and Hypothesis

To quantify the number of expired sample closet medications and to analyze the medications most commonly found for their novelty and usefulness. We hypothesized that the medications found in local sample closets will often be expired and will not be novel or useful.

Methods

We inventoried ten sample closets in primary care clinics. We quantified the number of expired medications and analyzed the 23 medications found in seven or more closets. To assess novelty, we determined if the sample medication: had a new mechanism of action, had a generic on market with same mechanism of action, and had a generic medication on market for the same indication. To assess usefulness, we determined if the sample medication had improved patient oriented outcomes, safety, and tolerability. We noted the cost of a one-month supply for the typical starting dose of each sample medication.

Results

Of the 12,581 drug packages and boxes we inventoried, 14% of were expired. Ninety-six percent (n=22) of sample closet medications had a generic medication on the market for the same indication and 74% (n=17) had a generic medication on the market with the same mechanism. Only 3 medications (13%) had evidence of superior patient oriented outcomes when compared to other medications for the same indication. Six medications (26%) demonstrated superior safety and tolerability. Only one medication (4%) was recommended as first line therapy in an evidence-based guideline. The mean cost for a one month supply of a typical starting dose was 178 dollars.

Significance and Conclusions.

Sample closet medications are often expired, have limited novelty and usefulness, and are expensive. The widespread use of sample medications should be re-examined.

Table of Contents.

Introduction/Significance	Page 1-3
Research Materials and Methods	Page 4-5
Results	Page 6-14
Discussion	Page 15-18
Future Directions	Page 19
Conclusions	Page 20
References	Page 21-25

List of figures and tables.

Table 1. Results of inventory of ten sample closets in Phoenix family medicine and internal medicine offices.	Page 8
Image 1. An example of a well organized drug sample closet with no expired medications.	Page 9
Image 2. An example of a poorly organized drug sample closets, with many expired medications.	Page 10
Table 2. Characteristics of the most commonly found medications in sample closets.	Page 11
Table 3. Cost of the most commonly found medications in sample closets.	Page 12
Table 4. Medications most commonly found in sample closets and the relevant guideline to evaluate usefulness.	Page 13
Figure 1. Percentage of yes and no answers regarding novelty and usefulness of most commonly found sample drugs.	Page 14

Introduction/significance.

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 encounters² and 12% of the U.S. population receive drug samples annually.³ In 2004, the pharmaceutical industry spent \$16.4 billion on the provision of sample drugs in the United States.⁴ 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.⁵ However, substantial evidence indicates that the use of sample medications is unlikely to benefit patients.

Physicians and office staff often use sample drugs for themselves or their families.⁶ 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 of at least 200% above the federal poverty line.³

The provision of medications without a pharmacist introduces safety concerns; pharmacists screen for drug interactions and are available to discuss use and side effects with patients.⁵ Physicians dispensing drug samples directly rarely provide such counseling. Physicians provide drug information with 48% of drug sample distributions, but the information primarily regards dosing and not side effects or drug interactions.² The use of sample medications that bypass office based electronic medical records increases the risk of unintended drug interaction.

Drug samples also have a negative impact on physician prescribing practices and on patient drug cost. Physicians are more likely to prescribe drugs that differ from their preferred drug choice and to deviate from the usual standards of care.^{5,7,8} The use of suboptimal therapy may lead to inferior care. For example, in one study, uninsured patients that used samples had

worse blood pressure control than those that did not.⁹ Although patients may perceive a financial benefit from “free” sample drugs, their out of pocket cost, due to subsequent prescription copayment expenses, is actually higher.¹⁰ The cost of prescription drugs in the United States continues to rise¹¹ and cost concerns are one of the most common causes of medication nonadherence.¹²

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.^{13,14} The frequency and consistency in which this maintenance is done is unknown. As a result, the presence of expired sample medications may be more prominent than we think. The contents of sample closets, including expired medications, have not been studied in depth in the United States. Estimates from a sample inventory in Australia indicate that 6% of sample medications may be expired.¹³

The therapeutic value of sample drugs has also been questioned. Drug samples are “almost never time worn and well-tested drugs...and usually comprise the newest drugs on the market.”¹⁵ Many new drugs on the market are “me too” drugs, a new drug within an existing class of medications, offering minimal additional therapeutic benefit.¹⁶ In addition, the long-term safety of newly approved drugs is often unknown.^{17,18} The sample closet is an important marketing tool for the pharmaceutical industry.¹⁹⁻²² Indeed, samples are one of industry’s “most potent marketing techniques.”¹⁵

Newly approved drugs, including those most likely to be found in samples closets, are often not novel or useful.¹⁰ For example, in one analysis of new drugs approved by the FDA in 2008, not a single new drug was both novel and relevant to primary care.¹⁶ 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 quantify the number of expired medication and analyze the medications most commonly found in sample closets to assess their novelty and usefulness in primary care practice. We hypothesize that the medications found in the sample closets will often be expired and will not be novel or useful for primary care physicians.

Research Materials and Methods.

We inventoried the drug sample closets of ten primary care offices in the Phoenix Metropolitan Area. We selected a convenience sample of teaching clinics for the University of Arizona College of Medicine's Longitudinal Clinical Experience curriculum that were known to have sample closets. We inventoried seven family medicine and three internal medicine offices. Six were group practices and four were solo practices. Five were hospital-affiliated and five 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 in 2009 and recorded drug sample name, quantity, expiration date, and dosage for each medication.

We independently assessed novelty and usefulness of the medications found in at least seven of the ten sample closets. To minimize bias, we included a nationally recognized expert on new medications for primary care in our deliberations (GS). We resolved differences by consensus. The three questions to assess the novelty of the medication were: Is the medication the first in a new drug class or does it work by a novel mechanism? Is there a generic medication already on the market with the same mechanism? Is there a generic medication already on the market for the same indication? The three questions to assess medication usefulness were: Do published randomized control trials (RCTs) or systematic reviews with patient oriented outcomes demonstrate that the medication is superior to medications already on the market for the same indication? Do comparative efficacy randomized controlled trials or systematic reviews demonstrate increased safety or tolerability compared to medications already on the market for the same condition or indication? Is the medication recommended as a first line agent in an evidence-based guideline?

We documented FDA approval year, indication, and drug mechanism. For the usefulness questions, we searched MEDLINE with limits on RCTs and systematic reviews, the National Guideline Clearinghouse (AHRQ), and the clinical reference tools DynaMed and Micromedex.

We estimated, with the help of an expert pharmacist (MA) the average wholesale price for a one month starting dose of each medication based on Price Alert, Drugstore.com, and the Pharmacists Letter.

Results.

The ten sample closets contained 12,581 individual medication sample packets/boxes with a mean of 1,258 (range 83-2,850) per closet. The ten closets had a mean of 123 different medications (range 6-241). Table 1 lists the mean, median, and range of sample boxes/packages per closet, expired boxes/packages per closet, and expired boxes/packages as a percent of the total. The number of samples, the organization of the closets, and the number of expired medications was highly variable between practices. Two closets had no expired medications on the day we inventoried. Better organized closets (see photo 1) were less likely to have expired medications. Poorly organized closets (see photo 2) were likely to have more expired medications, including one sample closet that had 28% expired medications.

Twenty-seven individual medications were common to at least seven of the ten sample closets. We excluded four of these twenty-seven medications from the study because they were combination drugs that fell into two separate medication classes (for example, Exforge, found in seven 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 as ezetimibe was the only novel drug in a combination medication. We also excluded non-prescription drugs, such as over the counter medications or herbal remedies (n=18) 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 2 lists those medications found in at least 7 of the 10 closets and the clinical indication. Table 3 lists the average monthly cost for the commonly used starting dose.

Figure 1 displays the proportion of the 23 medications that had novel or useful attributes, based on our six pre-specified questions.

Seventy-eight percent (n=18) of drugs 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 was on the market with the same mechanism. In nearly all cases, (96%, n=22) a generic medication was already on the market for the same indication. For 87% (n=20) of drugs, no RCTs or systemic reviews with patient oriented outcomes demonstrated superiority to medications already on the market for the same indication. For 74% (n=17) of the medications no published RCTs or systemic reviews demonstrating superior safety or tolerability. One (4%) of the medications is recommended as first-line therapy in an evidence-based guideline. Table 4, shows the guideline used to evaluate each medication.

The average wholesale price for one month of the most commonly used starting dose for each analyzed drug is shown in Table 3. 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 dollars, with a median of 158 dollars, minimum of 21 dollars, and maximum of 749 dollars. In 20 of 23 instances, a generic alternative was available at a commonly used pharmacy for four dollars per month.²³

Table 1: Results of inventory of ten sample closets in Phoenix family medicine and internal medicine offices.

	Mean	Median	Range	Total for 10 closets
Number of sample boxes/packages in closet	1,258	1,114	83-2,850	12,581
Number of expired boxes/packages in closet	170	96	0-796	1,698
Expired boxes/packages as % of total	10.4%	8.4%	0-28%	13.5%

Picture 1. An example of a well organized drug sample closet with no expired medications.



Picture 2. An example of a poorly organized drug sample closets, with many expired medications.



Table 2. Characteristics of the most commonly found medications in sample closets.

Trade Name	Generic name	Date Initially FDA Approved	# Sites containing sample	Indications
Bystolic	nebivolol	2007	9	Hypertension
Crestor	rosuvastatin	2003	9	Hyperlipidemia
Januvia	sitagliptin	2006	9	Type 2 Diabetes
Micardis	telmisartan	1998	9	Hypertension
Toviaz	fesoterodine	2008	9	Overactive Bladder
Avodart	dutasteride	2001	8	Benign Prostate Hyperplasia
Cymbalta	duloxetine	2004	8	Depression, Anxiety
Diovan	valsartan	2001	8	Hypertension
Lipitor	atorvastatin	1996	8	Hyperlipidemia
Lovaza	omega-3-acid ethyl esters	2004	8	Hypertriglyceridemia
Pristiq	desvenlafaxine	2008	8	Depression
Seroquel	quetiapine	1997	8	Schizophrenia, Bipolar Disorder
Actos	pioglitazone	1999	7	Type 2 Diabetes
Amitiza	lubiprostone	2006	7	Chronic idiopathic constipation
Celebrex	celecoxib	1998	7	Joint Pain
Enablex	Darifenacin	2004	7	Overactive Bladder
Levitra	vardenafil	2003	7	Erectile Dysfunction
Maxalt	rizatriptan	1998	7	Migraine Headache
Savella	milnacipran	2009	7	Fibromyalgia
Spiriva	tiotropium	2004	7	COPD
Synthroid	levothyroxine	2002	7	Hypothyroidism
Trilipix	fenofibric acid	2008	7	Hyperlipidemia, hypertriglyceridemia
Vytorin	ezetimibe and simvastatin	2004	7	Hyperlipidemia

Table 3. Cost of the most commonly found medications in sample closets.

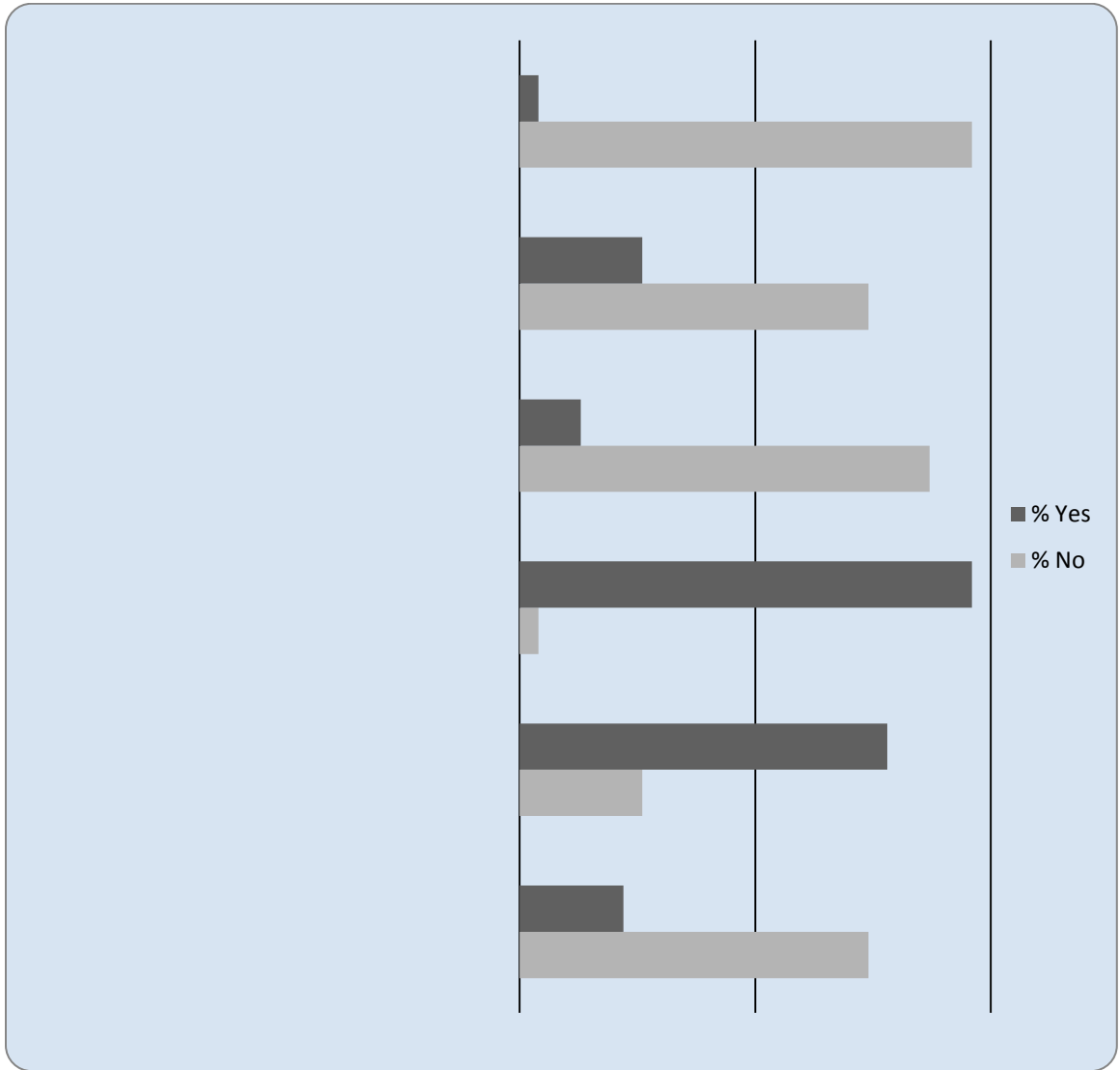
Trade Name	Most Common Initial Dose	AWP*
Bystolic	5mg daily	\$68 / 30 tabs
Crestor	10mg daily	\$157 / 30 tabs
Januvia	100mg daily	\$244 / 30 tabs
Micardis	40mg daily	\$124 / 30 tabs
Toviaz	4mg daily	\$159 / 30 tabs
Avodart	0.5mg daily	\$129 / 30 tabs
Cymbalta	60mg daily	\$183 / 30 caps
Diovan	80mg daily	\$97 / 30 tabs
Lipitor	20mg daily	\$183 / 30 tabs
Lovaza	4gm daily	\$190 / 120 1gm caps
Pristiq	50mg daily	\$153 / 30 tabs
Seroquel	200mg BID	\$749 / 60 tabs
Actos	30mg daily	
Amitiza	24mcg BID	\$272 / 60 caps
Celebrex	100mg BID	\$176 / 60 caps
Enablex	7.5mg daily	\$167 / 30 tabs
Levitra	10mg	\$21 / tab
Maxalt	5mg	\$32 / tab
Savella	50mg BID	\$146 / 60 tabs
Spiriva	1capsule (18mcg) daily	\$289 / 30 caps
Synthroid	100mcg daily	\$21 / 30 tabs
Trilipix	45mg daily	\$54 / 30 caps
Vytorin	10/20mg daily	\$148/ 30 tabs

*Cost of a 30-day supply of the most commonly used initial dose of the medication.

Table 4. Medications most commonly found in sample closets and the relevant guideline to evaluate usefulness.

Trade Name	Generic name	Relevant Guideline
Synthroid	levothyroxine	AACE 2002 ²⁴
Maxalt	rizatriptan	AAFP/ACP-ASIM 2002 ²⁵
Levitra	vardenafil	ACP 2010 ²⁶
Celebrex	celecoxib	ACR 2012 ²⁷
Januvia	sitagliptin	ADA 2012 ²⁸
Actos	pioglitazone	ADA 2012 ²⁸
Cymbalta	duloxetine	APA 2010 ²⁹
Pristiq	desvenlafaxine	APA 2010 ²⁹
Amitiza	lubiprostone	ASCRS 2007 ³⁰
Lovaza	omega-3-acid ethyl esters	ATP III 2004 ³¹
Crestor	rosuvastatin	ATP III 2004 ³¹
Lipitor	atorvastatin	ATP III 2004 ³¹
Trilipix	fenofibric acid	ATP III 2004 ³¹
Vytorin	ezetimibe and simvastatin	ATP III 2004 ³¹
Avodart	dutasteride	AUA ³²
Savella	milnacipran	EULAR 2008 ³³
Spiriva	tiotropium	GOLD 2010 ³⁴
Bystolic	nebivolol	JNC VII ³⁵
Micardis	telmisartan	JNC VII ³⁵
Diovan	valsartan	JNC VII ³⁵
Toviaz	fesoterodine	NICE 2006 ³⁶
Enablex	Darifenacin	NICE 2006 ³⁶
Seroquel	quetiapine	NICE 2006 ³⁷
<p>JNC = Joint National Committee, AUA= American Urologic Association, AAFP/ACP-ASIM= American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine, ATP = Adult Treatment Panel, NICE= National Institute for Clinical Excellence (UK), APA = American Psychiatric Association, GOLD = Global Initiative for Chronic Obstructive Lung Disease, EULAR=European League Against Rheumatism, ACR= American College of Rheumatism, ASCRS= American Society of Colon and Rectal Surgeons, AACE= American Association of Clinical Endocrinologists</p>		

Figure 1. Percentage of yes and no answers regarding novelty and usefulness of most commonly found sample drugs.



Discussion.

In this study, we found that the medications most commonly found in drug sample closets are frequently expired, are rarely novel or useful, and are expensive.

Thirteen and a half percent of sample closet medications were expired. In offices that had few expired medications we were unable to quantify the number of medicines removed from the closets prior to our inventory. It is likely that our tally underestimates medication waste as some practices dispose of medications on a regular basis.

We hypothesize that there are two main reasons sample closets contain substantial numbers of expired medications. First, the presence of expired medications may be due to the absence of a reliable inventory system in most practices. Indeed, in a qualitative study of 18 family practice offices, Backer and colleagues described a wide variety of sample closet organization systems from “an extraordinary and meticulously organized shelving system,” to a closet that was an “overfilled, disorganized stack of shelves,” where “staff spent vast amounts of time searching for the appropriate sample.”² Second, the supply of individual medications, provided by pharmaceutical representatives as part of a marketing effort, may not match well with medications physicians prefer to use in practice.³⁸ Regardless of cause, expired samples are not useful to patients and are a waste of resources. Our findings extrapolate to an estimated \$2.2 billion of wasted samples in the United States annually.

In regards to the most commonly found medications, only five of the twenty-three 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.³⁹ For example, HMG CoA reductase inhibitors rosuvastatin and atorvastatin were found in nine and eight sample closets, respectively. These drugs are among eight “statin” drugs on the market, including three that are currently available generically.³⁹ Samples

are an important marketing tool of industry. The finding that 78% of these drugs are “me too” drugs confirms the hypothesis by Brody and Light that “the ratio of benefits to harms among patients taking new drugs tends to vary inversely with how extensively the drugs are marketed.”⁴⁰ All medications except one medication, vardenafil, have a generic on the market for the same indication.

In addition to a lack of novelty, we have shown that commonly sampled medications are often not useful. To be useful, a medication should be safer or more effective than existing medications 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 (i.e. blood pressure). When studies exist of clinically meaningful outcome measures, these studies commonly compare the drug only to placebo rather than to existing medications.⁴¹

We also question the usefulness of sample medications based on our finding that 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 medication. Often, the incremental improvement in tolerability or safety existed only in a limited number of industry-funded studies. For example, we designated darifenacin as better tolerated than oxybutynin based on a single small industry-funded study.⁴² In this study, differences in dry mouth existed only when comparing darifenacin 15mg daily with oxybutynin 5 mg.⁴² Darifenacin 30mg had a similar rate of dry mouth to oxybutynin 5 mg three times per day. 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, the usefulness of the medication to clinicians is doubtful.

We have also shown that medications found most commonly in sample closets are not 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.”⁴³ 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 (JNC-7) guidelines for the evaluation and treatment of hypertension³⁵ address the 3 medications approved for hypertension (nebivolol, telmisartan, and valsartan) and the National Institute for Clinical Excellence (NICE) overactive bladder guideline³⁶ discusses the two 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, there is a generic equivalent, levothyroxine, which is equivalent⁴⁴ and less expensive.

When compared to 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 four dollars per month in selected “big box” and retail pharmacies. After a supply of “free” samples is depleted, a patient will often continue the same medication at a higher cost to both the patient and the healthcare system.¹⁰ In addition to the patient-level cost, this non-rational use of expensive medications costs the U.S. health system billions of dollars annually.¹⁵ For example, the use of brand name cholesterol lowering medications, instead of generics, costs the U.S health care system \$5.8 billion dollars annually.⁴⁵ Additionally, non adherence is common when the cost to the patient is high; this has the potential to increase morbidity.^{12,46,47}

There are several limitations to our study. First, our study is a small cross-sectional study in one metropolitan area. It is possible that the closets we inventoried are not representative of sample closets nationwide. Second, the six 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. Third, there is the potential for unintended bias as our rationale for performing this study arose from our skepticism of the novelty and usefulness of sample closet medications. Finally, while we performed a careful literature search to identify relevant practice guidelines, it is possible that we have overlooked guidelines that would have changed some of our conclusions.

Based on compelling evidence that sample medications are most commonly no safer or more effective than less expensive alternatives, many have called for the cessation of the sample distribution.^{15,20,48-50} According to Chimonas and Kassirer: “The tradition of physicians dispensing samples has many serious disadvantages and is as anachronistic as bloodletting and high colonic irrigations.”¹⁵ Indeed, many physicians have already 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.^{15,51}

What are the alternatives to a sample closet? Physicians should consider non-pharmacologic 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.⁴⁷ Erickson and Cullison have proposed a low-cost, physician-sponsored closet of generic medications for patients in need.⁴⁸ “Counter detailing” by local and national experts provides an alternative to pharmaceutical detailing.⁵²⁻⁵⁴ Additionally, non-profit organizations catalog existing pharmaceutical company sponsored patient assistance programs⁵⁵ and disease-specific assistance programs.⁵⁶

Future Directions.

There are a number of potential future directions for researching sample closet use in primary care.

First, since our results are from a small cross-sectional study in one metropolitan area, a further study inventorying sample closets across a greater variety of practices in both urban and rural settings throughout the United States, as well as academic and private practice settings would be useful to determine if our results can be generalized.

Second, correlating drug sample inventories with office maintenance logs could be useful to help determine the actual number of sample medications that go to waste.

Third, the sample closet inventories could be updated regularly to see if novelty and usefulness changes over time with new drugs on the market. It would be interesting to note how drug samples correlate with sales figures of new medications to determine a possible relationship between sample closet medications and marketing. Following sample medications over time could also reveal information about which highly marketed drugs were shown to be unsafe and removed from the market.

Fourth, qualitative and/or quantitative data could be gathered to determine how physicians use sample closets and how they feel these medications benefit their patients or practice. Why do physicians continue to heavily use samples when there is substantial evidence that patients do not benefit?

Fifth, our study methods could be expanded to the offices of specialties beyond internal medicine and family medicine, and sample closet characteristics could be compared across specialties.

Conclusions.

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

References.

1. Campbell EG, Rao SR, DesRoches CM, et al. Physician professionalism and changes in physician-industry relationships from 2004-2009. *Arch Int Med* 2010;170:1820-1826.
2. Backer EL, Lebsack JA, Van Tonder RJ, Crabtree BF. The value of pharmaceutical representative visits and medication samples in community-based family practices. *J Fam Pract* 2000;49:811-816.
3. 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;98:284-289.
4. Kaiser Family Foundation. Prescription drug trends, Fact Sheet 3057-04, November 2005. Available at: <http://www.kff.org/insurance/upload/3057-04.pdf>. Accessed April 25, 2012.
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;15:478-483.
6. Westfall JM, McCabe J, Nicholas RA. Personal use of drug samples by physicians and office staff. *JAMA* 1997; 278:141-143.
7. Symm B, Averitt M, Furjuoh SN, Preece C. Effects of using free sample medications on the prescribing practices of family physicians. *J Am Board Fam Med* 2006;19:443-9.
8. Adair RF, Holmgren LR. Do drug samples influence resident prescribing behavior? A randomized trial. *A J Med* 2005;118:881-4.
9. Zweifler J, Hughes S, Schafer S, Garcia B, Grasser A, Salazar L. Are sample medicines hurting the uninsured? *J Am Board Fam Pract* 2002;15:361-6.
10. 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;46:394-402.
11. Kaiser Family Foundation. Prescription drug trends, Fact Sheet 3057-08, May 2010. Available at: <http://www.kff.org/rxdrugs/upload/3057-08.pdf>. Accessed April 25, 2012.

12. Piette JD, Heisler M, Wagner TH. Cost-related medication underuse: Do patients with chronic illnesses tell their doctors? *Arch Intern Med* 2004;164:1749-1755.
13. Hall KB, Tett SE, Nissen LM. Perceptions of prescription medicine samples on prescribing by family physicians. *Med Care* 2006;44:383-387.
14. Cohen ML. Taming the sample closet. *Fam Pract Manag* 2006;13:43-6.
15. Chimonas S, Kassirer JP. No more free drug samples? *PLoS Med* 2009;6:e10000074.
16. Smetana GW, Sillman JS. Update in new medications for primary care. *J Gen Intern Med* 2009;24:111-7.
17. Anderson GM, Juurlink D, Detsky AS. Newly approved does not always mean new and improved. *JAMA* 2008;299(13):1598-1600.
18. Friedman MA, Woodcock J, Lumpkin MM, Shuren JE, Hass AE, Thompson LJ. The safety of newly approved medicines: do recent market removals mean there is a problem? *JAMA* 1999;281:1728-34.
19. Mizik N, Jacobson R. Are physicians “easy marks”? Quantifying the effects of detailing and sampling on new prescriptions. *Management Science* 2004;50:1704-15.
20. Brown SR. Closing the sample closet. *Fam Pract Manag* 2006;13:16-21
21. Kyle GJ, Nissen LM, Tett SE. The Australian rise of esomeprazole- was expenditure on samples a contributor? *Pharmacoepidemiol Drug Saf* 2009;18:62-8.
22. 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;28:259-71.
23. Target pharmacy. \$4 drug program information. Available at:
http://sites.target.com/site/en/spot/page.jsp?title=pharmacy_generic_drugs_condition.
Accessed April 25, 2012.
24. Baskin HJ, Cobin RH, Duick DS, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract* 2002;8:457-69.
25. Snow V, Weiss K, Wall EM, Mottur-Pilson C; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic

- management of acute attacks of migraine and prevention of migraine headaches. *Ann Intern Med* 2002;137:840-9.
26. Qaseem A, Snow V, Denberg TD, et al. Hormonal testing and pharmacologic treatment of erectile dysfunction: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2009;151:639-49.
 27. Hochberg MC, Altman RD, April K, et al. American College of Rheumatology 2012 recommendations for the use the nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care and Research* 2012;64:465-474.
 28. American Diabetes Association. Standards of Medical Care in Diabetes 2012. *Diabetes Care* 2012; 35: S11-63.
 29. American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct. 152 p.
 30. Ternent CA, Bastawrous AL, Morin NA, et al and The Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice parameters for the evaluation and management of constipation. *Dis Colon Rectum* 2007;50:2013-22.
 31. Grundy SM, Cleeman JI, Merz CN, et al. National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.
 32. McVary KT, Roehrborn CG, Avins BL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol* 2011;185:1793-803.
 33. Carville SF, Arendt-Nielsen S, Blotman F, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis* 2008;67(4):536-41.
 34. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2010. 96 p.

35. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;42:1206-42.
36. National Institute for Clinical Excellence. Urinary incontinence: The management of urinary incontinence in women. Available at: <http://www.nice.org.uk/cg40>. Accessed April 25, 2012.
37. National Institute for Clinical Excellence. Bipolar disorder: The management of adults, children, and adolescents in primary and secondary care. Available at www.nice.org.uk/cg038. Accessed April 30, 2012.
38. Spurling G, Kyle G. Is your sample cupboard relevant to your practice? *Aust Fam Physician* 2007;36(3):187-8.
39. Gagne JJ, Choudhry NK. How many “me-too” drugs is too many? *JAMA* 2011;305:711-12.
40. Brody H, Light DW. The inverse benefit law: how drug marketing undermines patient safety and public health. *Am J Public Health* 2011;101:399-404.
41. Goldberg NH, Schneeweiss S, Kowal MK, Gagne JJ. Availability of comparative efficacy data at the time of drug approval in the United States. *JAMA* 2011;305:1786-9.
42. Zinner N, Tuttle J, Marks L. Efficacy and tolerability of darifenacin, a muscarinic M3 selective receptor antagonist, compared with oxybutinin in the treatment of patients with overactive bladder. *World J Urol* 2005;23:248-252.
43. Institute of Medicine. Clinical practice guidelines we can trust. March 23, 2011. Available at: <http://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx>. Accessed April 25, 2012.
44. Dong BJ, Hauck WW, Gambertoglio JG, et al. Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. *JAMA* 1997;277:1205-13.
45. Kale MS, Bishop TF, Federman AD, Keyhani S. “Top 5” lists top \$5 billion. *Arch Intern Med* 2011;171:1856-1858.

46. Madden JM, Graves AJ, Zhang F, et al. Cost-related medication nonadherence and spending on basic needs following implementation of Medicare Part D. *JAMA* 2008;299:1922-1928.
47. Sagall RJ. Can your patients afford the medications you prescribe? *Fam Pract Manag* 2006;Apr:67-69.
48. Erickson SH, Cullison S. Closing the sample closet. *Fam Pract Manag* 1995;October:43-47.
49. Brennan TA, Rothman DJ, Blank L, et al. Health industry practices that create conflicts of interest: a policy proposal for academic medical centers. *JAMA* 2006;295:429-33.
50. Puget Sound Health Alliance. Position statement on use of pharmaceutical samples in practice locations.
http://www.pugetsoundhealthalliance.org/services/documents/HealthAlliancePosition_RxSamples_053006.pdf. Accessed April 25, 2012.
51. Fugh-Berman A, Brown SR, Trippett R, et al. Closing the door on pharma? A national survey of family medicine residencies regarding industry interactions. *Acad Med* 2011;86:649-54.
52. O'Brien MA, Rogers S, Jamtvedt G, et al. Educational outreach visits: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev* 2007;4:CD000409.
53. Allen M, Ferrier S, O'Connor N, Fleming I. Family physicians' perception of academic detailing: a quantitative and qualitative study. *BMC Med Educ* 2007; 7:36.
54. Avorn J. Teaching clinicians about drugs – 50 years later, whose job is it? *NEJM* 2011;364:1185-7.
55. Choudhry NK, Lee JL, Agnew-Blais J, Corcoran C, Shrank WH. Drug company-sponsored patient assistance programs: A viable safety net? *Health Affairs(Milwood)* 2007;28:827-34.
56. NeedyMeds. Disease-based assistance. Available at:
http://www.needymeds.org/copay_branch.taf. Accessed April 25, 2012.