2015

ECONOMIC IMPACT OF WASTE IN PRESCRIBING, DISPENSING, AND MEDICATION CONSUMPTION IN THE UNITED STATES

Sarah Almanie
Virginia Commonwealth University

ECONOMIC IMPACT OF WASTE IN PRESCRIBING, DISPENSING, AND
MEDICATION CONSUMPTION IN THE UNITED STATES

A thesis submitted in partial fulfillment of the requirements for the degree of Master of
Science at Virginia Commonwealth University.

by

Sarah A. Almanie
BS 2006
Kuwait University

Director: David A. Holdford, R.Ph., M.S., Ph.D., FAPhA
Professor
Department of Pharmacotherapy and Outcomes Science

Virginia Commonwealth University
Richmond, Virginia
May, 2015

Dedication

This thesis is dedicated to the two precious persons in my life, my mother, who prayed for me continually, and my husband "Mohammad", who supported me in every single moment. Thanks God for blessing me with such people in my life.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ABMS: Appointment based medication synchronization

AP: Associated Press

CDC: Centers for Disease Control

CINHAL: Cumulative Index to Nursing and Allied Health Literature

CPT: Current Procedural Terminology

IPA: International Pharmaceutical Abstracts

MCBS: Medicare Current Beneficiary Survey

MEPS: Medical Expenditure Panel Survey

MS: Multiple Sclerosis

NAMCS: National Ambulatory Medical Care Survey

NCPA: National Community Pharmacists Association

NHAMCS: National Hospital Ambulatory Medical Care Survey

OTC: Over the Counter

P3C   Pharmacists for the Protection of Patient Care

PSA: Probabilistic Sensitivity Analysis

RTS   Returned to Stock

TNF: Tumor Necrosis Factor

VAPAHCS: Veterans Affairs Palo Alto Health Care System

Abstract

ECONOMIC IMPACT OF WASTE IN PRESCRIBING, DISPENSING, AND
MEDICATION CONSUMPTION IN THE UNITED STATES

By Sarah A. Almanie, M.S.

A thesis submitted in partial fulfillment of the requirements for the degree of Master of
Science at Virginia Commonwealth University.

Virginia Commonwealth University, 2015.

Major Director: David A. Holdford, R.Ph., M.S., Ph.D., FAPhA
Professor
Department of Pharmacotherapy and Outcomes Science

OBJECTIVES: This research examines waste associated with the medication use

process which consists of unfilled prescriptions, abandoned prescriptions, or unused

prescription medications. The aim of this study is to quantify the direct medical costs of

medication waste in delivery of care in the United States.

METHODS: A review of published literature and data from the 2012 Medical

Expenditure Panel Survey was used to quantify the number of prescriptions wasted at

different stages of the medication prescribing and use process and the associated costs

were calculated.

RESULTS: In 2012, more than 26 million prescriptions were either unfilled or abandoned, and more than 225 million resulted in dispensed medications that were not used. The total cost of this waste was estimated at $30.4 billion.

CONCLUSIONS: Patients who do not fulfill their role in the medication use process cause significant, avoidable costs to the health care system beyond the health outcomes not achieved.

Chapter 1

Section1.1: Background

Medicines constitute a major role in the treatment of many diseases; however, not all medications are consumed by patients. When they are not consumed, they are wasted and can become a risk to humans and the environment. The risks of drug waste come from three primary sources: storage, disposal, and nonuse.

Storage

Improperly stored medications in households can cause harm in several ways. One way is that children may accidentally ingest medications stored in the home and be poisoned. Another way is by diversion of stored medications for recreational use. This can occur when young family members experiment with other family members' controlled substances or when leftover medications are shared with friends or family members. Finally, stored medicines in the home provide an option for suicide attempts among individuals.

Studies support the potential harm from stored medications. A survey of emergency room visits revealed that the number of visits due to non-medical use of prescription drugs and over the counter medications equaled 1.2 million in 2009, half of which

1

was attributed to opioid analgesics.[1] A report from the centers for disease control (CDC) in 2009 also showed that about 91% of unintentional poisoning deaths in the U.S. were caused by drug overdoses, commonly, prescription opioids.[2]

Disposal

Drug disposal is another risk from drug waste. Improper disposal of drugs can make it into the sewage system and eventually the nation's water supply. A report from the Associated Press showed that prescription drugs were found in the drinking water for 24 major metropolitan areas across the United States.[3] Analysts attributed such water contamination to the improper disposal of unused medications by humans. Another study in New York state investigated the presence of pharmaceuticals in two wastewater treatment plants between the years 2004-2009 and found that processed wastewater from factories contained high concentrations of opioids and muscle relaxants.[4] Although the risk to humans of drugs in groundwater is not clear, the impact on marine mammals is more apparent. In 2012, the U.S. geological survey reported a high prevalence of fish intersex was seen in the Potomac River watershed. Fish intersex occurs when female fish experience male characteristics and vice versa. Investigators related such mutations to the presence of hormonal medicines in water.[5]

Nonuse

Opportunity costs are associated with prescribed medications that are not used by patients as directed. A report from IMS Health, revealed that around $213 billion in the United States was wasted in 2012 on prescribed medications. A breakdown of costs showed that approximately half of these avoidable costs were associated with patients

who don't refill their medications, don't take their medications as directed, or develop health complications requiring treatment.[6]

Other research illustrates the costs of medication waste. In a single hospice program (2005), it was found that the average cost of medications left at death by 100 patients was between $100 and $200 per patient.[7] In 2010, the total amount of prescribed medications collected in a national prescription take back event was more than 121 tons.[8]

Defining "Medication Waste"

The literature provides no consistent definition of medication waste, making it difficult to quantify the problem and compare studies. According to Oxford dictionary, "waste" is defined as "an act or instance of using or expending something carelessly, extravagantly, or to no purpose".[9] This definition indicates that anything that is used carelessly, inefficiently, or ineffectively is waste.

In the literature, medication waste has a variety of definitions. These include:

1. "medicines issued to the patient but not consumed",[10]

2. "any drug product, either dispensed by a prescription or purchased over the counter (OTC), that is never fully consumed",[11]

3. "items which have been dispensed but are unused or partly used by patients and eventually need to be disposed",[12]

4. "the consequence of an inappropriate disposal of unused or partially used ampoules, vials, or syringes of drugs",[13]

3

5. and "medication that has been spilled, has been rejected for use by the patient, or otherwise cannot be returned to the pharmacy for reuse".[14]

There is a general agreement among these definitions that describes medication waste as unconsumed or unused medications. However, the definitions differ in the types of medications being wasted, the intended population, the underlying cause of wastage, and the way medicines are wasted. Some definitions include over the counter medications while others are limited to prescription medications. Certain definitions focus on outpatient populations and others target inpatient medication waste. Some definitions are limited to waste caused by a patient's refusal to take the medication or a left over dose while others are non-specific. Definitions also vary in how medications are wasted (e.g., improper disposal).

The consequences of medication waste are another source of variation in the literature. Studies of medication waste differ on the degree to which they examine impact on health outcomes, health of environmental ecosystems, and financial costs after being dispensed by pharmacy personnel. In addition, costs incurred prior to dispensing are not quantified such as preparation costs for each medication not picked up by a patient. In these cases, waste of labor occurs.

This research provides an operational definition of medication waste that focuses on medication use in community settings but expands on the definition of waste to include cost of labor. In this study, medication waste is defined as:

"resource use associated with unfilled, abandoned prescriptions and prescription medications that are not consumed by patients in the community".

4

This definition focuses on medication use that is primarily within the control of the end consumer (patients) and excludes waste in institutional settings which may occur for reasons unrelated to patient actions (e.g., spilled chemotherapy, changes in medication orders resulting in disposal). In the community, patients make most decisions on where to store medications, how to dispose of them, and whether to take them or not. In institutional inpatient settings, these choices are typically up to health care professionals.

The basic elements of medication waste in this study's definition are unfilled prescriptions, abandoned prescriptions, and unused prescription medications in outpatient settings. **Unfilled prescriptions** are those which are prescribed but not transmitted to the pharmacy for preparation. Unfilled prescriptions waste the time and resources of prescribers and their support personnel -- time that can be spent on productive activities, i.e. opportunity cost. **Abandoned prescriptions** are transmitted or delivered to the pharmacy but not picked up by the patient. They waste time and resources of both prescribers and pharmacy personnel. **Unused prescription medications** are dispensed but not taken by patients as directed. They waste time and efforts of prescribers and pharmacy personnel, and they waste medications.

5

Section 1.2: Objectives

The main aim of the study is to estimate the direct medical costs in the United States associated with unfilled prescriptions, abandoned prescriptions, and unused prescription medications in outpatient settings, excluding any impact on health outcomes. Thus, our study focuses on wastage in delivery of care but not the impact on patient health outcomes. The population of interest is ambulatory (out-patient) individuals who receive their medications in community pharmacy settings in the United States including pharmacy chains, independent pharmacies, mail order, large discount department and warehouse stores, grocery stores, outpatient clinics, specialty pharmacies, emergency department pharmacies. Hospital pharmacies that serve inpatients and long term care pharmacies were excluded from the study because they represent a separate setting which is subjected to different rules and regulations.

6

Specific aim I:

To estimate the annual direct medical costs of medication waste in delivery of care as a result of unfilled and abandoned prescriptions.

Specific aim II:

To estimate the annual direct medical costs of medication waste in delivery of care as a result of unused prescription medications.

7

Section 1.3: Rationale

Medication waste is a worldwide problem that is not only associated with financial impact. It also negatively impacts safety, health and environment. Better understanding the problem can enable the healthcare system, patients and society to intervene and minimize the scope of the problem. Our study will contribute to the literature by examining medication waste from a different perspective. It will study the wasted inputs of the medication delivery system.

Section 1.4: Conceptual Framework

Waste associated with the medication use process consists of any written prescriptions that are (1) not taken to a pharmacy to be filled, (2) taken to be filled but abandoned at the pharmacy, or (3) dispensed but not consumed as directed. The economic burden of medication waste is assessed from a societal perspective. When a societal perspective is used, three main types of costs are typically considered: direct costs, indirect costs, and intangible costs (summarized in Table 1.1). However, in the current study we are interested in waste in medication therapy delivery so, only physician visit costs, dispensing costs, and prescription ingredient costs will be examined. In other words, this research focuses on input costs associated with delivery of medication therapy to patients (e.g., waste in time and effort, drugs) and excludes output costs resulting from the delivery of medications (e.g., resource use associated with negative health outcomes, lost productivity, , mortality, and morbidity). Figure 1.1 illustrates the conceptual model used in this study.

9

Table 1.1 Types of costs associated with societal perspective

Type of cost	Example	Costs related to our research
Direct medical cost associated with delivery of medication therapy	Input costs: - Outpatient physician's visit cost - Dispensing cost - Prescription cost*	✔ ✔ ✔
Direct medical cost associated with failures in medication therapy	Output costs**: - Hospitalization cost - Emergency department visit cost - Outpatient physician's visit cost - Pharmacy cost	
Direct non-medical cost	Transportation cost Disposal cost	
Indirect cost	Loss of productivity	
Intangible cost	Feeling Dissatisfaction Confusion	
Other societal cost	Environmental cost	

* Prescription cost = dispensing cost + ingredient cost
**Costs related to deterioration in health condition associated with medication waste

The first step in the model occurs when a physician prescribes a medication for use by a patient. In many cases, the prescription is sent electronically, by phone, or by fax transmission to be automatically prepared (filled) by the pharmacist for pickup by the patient. In some cases, the physician gives the patient a hand written prescription to be dropped off at a pharmacy. Many of these prescriptions are taken to the pharmacy to be filled but not all of them. Some are never taken by the patient to be filled in a pharmacy (not filled). Prescriptions that are delivered and filled at the pharmacy can either be

المنارة للاستشارات

www.manaraa.com

dispensed to the patient (picked up) or left at the pharmacy by the patient (abandoned). A prescription that is abandoned for a defined period of time (usually two weeks) will be returned to stock. If the patient picks up the prescription from the pharmacy, the prescribed medication will either be used as directed (used) or not used as directed (not used). Medications that are not used as directed may be used in way that was not prescribed or they may not be used at all.

At each step of the prescription writing and filling process, costs are incurred due to personnel time and effort, supplies, and medication. Any resources used that do not result in a medication being taken as directed are considered waste. In the base case of this model, refill orders which don't require a physician visit are not considered.
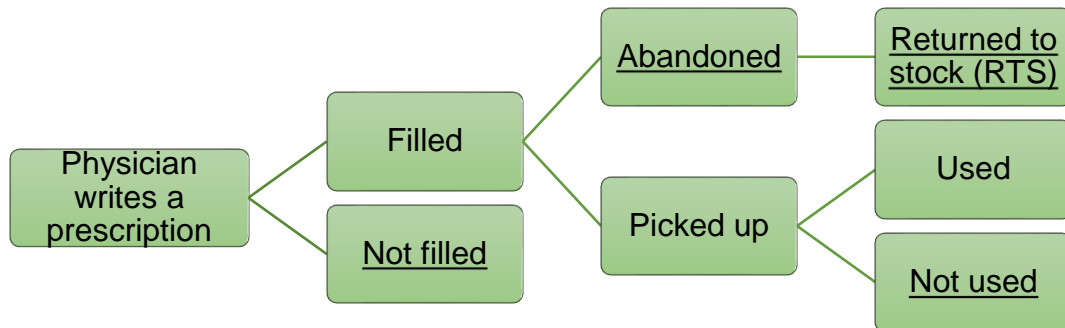
Figure1.1 Model of the medication use process: underlined words represent points where direct medical costs are incurred.

Chapter 2

Systematic Literature Review on the Economic Burden of Medication Waste

A systematic literature review on the economic burden of medication prescriptions waste was completed on October, 2014. The three databases examined were PubMed/MEDLINE (limited to abstract available, English, and humans), Cumulative Index to Nursing and Allied Health Literature (CINHAL) and International Pharmaceutical Abstracts (IPA). The following inclusion and exclusion criteria were considered in the literature search:

Inclusion criteria

Original studies that:

1. Evaluated costs attributed to medication prescriptions waste (prescriptions not taken to a pharmacy to be filled, taken to be filled but abandoned at the pharmacy, or dispensed but not consumed as directed)

2. Quantified the rate or prevalence of unfilled prescriptions, abandoned prescriptions, and prescriptions dispensed but not consumed as directed

3. Identified reasons or predictors of medication prescription waste

4. Assessed patient, providers, and prescriptions characteristics associated with medication prescriptions waste

12

Exclusion criteria:

1. Evaluated environmental or safety/health related effects of medication waste

2. Research was not conducted in the United States

3. Evaluated medication waste for inpatient hospital settings, nursing homes and long term care facilities

4. Studied pediatric populations: this population was excluded because the current research focuses on patient role in leading to medication waste and children have a minimum or no control on their actions

The literature review was divided into two parts. The first part reviewed the literature on unfilled and abandoned prescriptions. The second part reviewed literature on medications that are picked up but not consumed as directed.

Part 1: Literature review of unfilled and abandoned prescriptions

Search terms used are summarized in Table 2.1. Titles and abstracts of articles were checked for inclusion and exclusion criteria. The original 1499 articles were reduced to 75 after applying inclusion and exclusion criteria and eliminating duplicates.[15-89] Of these, 11 articles were selected for discussion based on the following criteria:

- Evaluated cost of unfilled prescriptions, abandoned prescriptions, or unconsumed prescription medications

- Most recent studies

- Not specific to a disease condition

- More general settings compared to other studies

13

References from the included articles were also reviewed, yielding two relevant studies.[90,91] Literature search and selected articles are summarized in Figure 2.1 and Table 2.2, respectively.

Table 2.1 Search terms history for unfilled and abandoned prescriptions

Search term	Eligible articles		
	PubMed	CINHAL	IPA
Primary non-adherence	6	3	1
Abandoned prescriptions	3	3	2
Unfilled prescriptions	2	2	3
Unclaimed prescriptions	8	1	27
Filling and prescriptions	21	13	21
Cost and abandoned prescriptions	2	1	1
Costs and abandoned prescriptions	1	-	1
Cost and primary non adherence	1	-	-
Costs and primary non-adherence	1	-	-
Cost and abandoned and prescriptions	2	1	1
Costs and abandoned and prescriptions	1	-	1
Total unique eligible articles			75
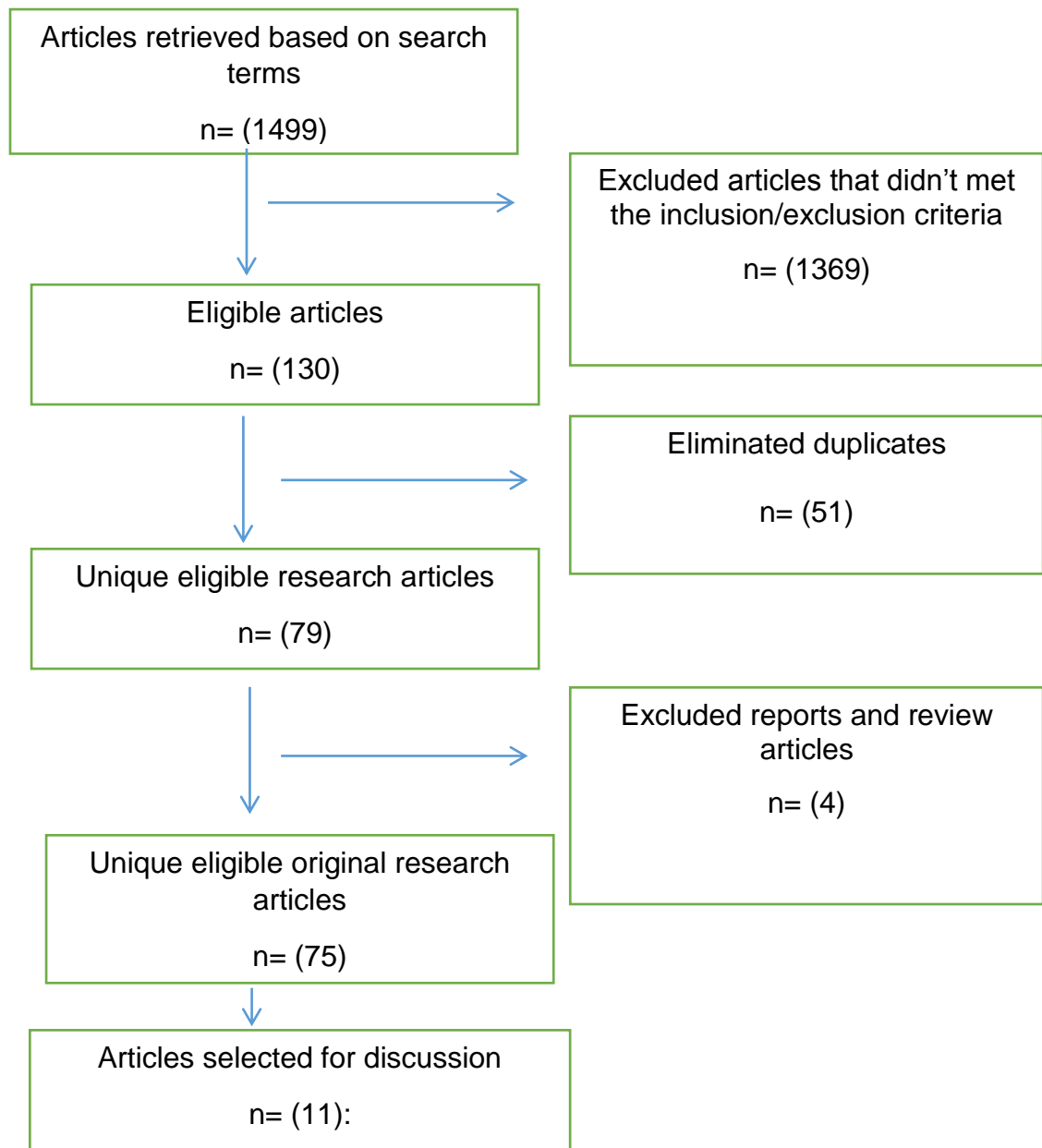
Figure 2.1 Flow chart summary of literature search*

*Adapted from: Sattler EL, Lee JS, Perri M,3rd. Medication (re)fill adherence measures derived from pharmacy claims data in older Americans: a review of the literature. Drugs Aging. 2013;30:383-399.

Table 2.2 Summary of included articles of unfilled and abandoned prescriptions

Author	Study design and sample	Sample size	Outcome measure of interest to our model	Period	Setting and data source	Findings relating to our research
Shrank et al 2010	- Cross sectional cohort study - All filled prescriptions within 3 months period	10,349,139 prescriptions	Rate of: 1. Picked-up prescription 2. Abandoned prescription with RTS* 3. Abandoned prescription with RTS* then fill	Two weeks	- CVS retail pharmacy chain - Pharmacy data (CVS) - PBM data (Caremark)	- Total abandoned prescriptions: 3.27% - Abandoned prescription with return to stock: 1.77% - Abandoned prescription with return to stock then filled: 1.5%
Bergeron et al 2013	- Cross sectional survey - Adults (≥ 18 years old)	344 patients	Rate of primary non-adherence before and after electronic prescribing	Patients follow up interviews occurred between 6 – 14 days after physician's visit	- One ambulatory care clinic - Discharge summary and patient's phone interview	- Primary non adherence rate: - 6.9% before e-prescribing - 10.6%, 6 months after e-prescribing - 2.5%, 12 months after e-prescribing
Streeter et al 2011	- Cross sectional cohort study - Cancer patients with new prescription for an	10,508 patients	Rate of prescription abandonment for newly initiated oral	90 days	Pharmacy claims database	- Prescription abandonment rate = 10%

17

	oral oncolytic agent		oncolytic agent (reversed claims)			
Gleason et al 2009	- Cross sectional study - Patients with newly initiated MS therapy or TNF blocker agent	10,104 patients	Association between out of pocket OOP payments and rate of prescription abandonment for newly initiated MS or TNF blocker therapy (reversed claims)	90 days	Pharmacy claims database	- Prescription abandonment rate increased as OOP payments increased: - MS therapy: (5.7 %– 28.5%) - TNF blocker: (4.7% - 26.4%)
Papke JA 1999	- Cross sectional study - New prescriptions that are filled (prepared), but unclaimed	18,233 prescriptions	Rate, and cost of unclaimed prescriptions	5 days	-Outpatient hospital pharmacy - Hospital database and patients' interview	- Rate of unclaimed prescriptions = 4.72% - Cost/unclaimed prescription = $4.99
Fischer et al 2010	- Cross sectional cohort study	195,930 prescriptions	Rate of primary non-adherence	Open period (until the end of data collection period)	- Outpatient clinics - Electronic prescribing transactions - Pharmacy claim	- Rate of primary non-adherence= 28.3%

					database	
Jackson et al 2014	- Cross sectional cohort study - New prescriptions for chronic diseases	29,238 prescriptions	Rate of primary medication non-adherence	30 days	- 100 retail pharmacies - A large national pharmacy chain database	- Rate of primary medication non-adherence = 12.2%
Reabel et al 2012	- Cross sectional cohort study - Patients with newly initiated prescriptions for an antihypertensive, antidiabetic, or antihyperlipidemic medication	12,061 patients	Rate of primary non-adherence	30 days	- Integrated healthcare system - Electronic medical records - Pharmacy information management system	- Rate of primary non-adherence: - 7% for antihypertensive group - 11% for antidiabetic group - 13% for antihyperlipidemic group
Shin et al 2012	- Cross sectional cohort study - Newly initiated electronic prescriptions for acute and chronic diseases	569,095 prescriptions	Rate of primary medication non-adherence	14 days	-Pharmacies at 14 medical centers - Electronic medical records	- Overall primary non-adherence rate = 9.8%
Kennedy et al 2008	- Cross section survey - Medicare beneficiaries aged	14,464 patients	Rate of unfilled (abandoned) prescriptions	Undetermined	- Medicare Current Beneficiary Survey	- Overall rate of unfilled prescriptions = 4.4%

19

					(MCBS) 2004 data	
Fischer et al 2011	-Cross sectional study - All patients having CVS Caremark's PBM drug coverage	423,616 prescription	Rate of primary non-adherence	Up to six months after prescribing	-Outpatient settings - Electronic prescribing database - pharmacy benefit management database	- Rate of primary non-adherence = 24%
Ding et al 2013	-Cross sectional study - Patients aged ≥ 18 years old discharged from emergency department with Medicaid coverage	1026 patient	Determine the validity of self-reported primary non-adherence (new and refill prescriptions)	30 days	- Emergency department at three hospitals - Medicaid pharmacy claims database - Emergency department information system - Patients' interview	- Rate of primary non-adherence = 26% - Patients' reported data had high sensitivity; however, low specificity: - Sensitivity: report filling a prescription for prescriptions with pharmacy claims - Specificity: report not filling a prescription for prescriptions without pharmacy claims

Thomas et al 2006	- Cross sectional survey - Adults ≥18 years	3,926 patients	Primary non-adherence (new and refill prescriptions)	Undetermined	- Medical care centers in rural areas of 8 southeastern states	- 21.6% delay or not fill a prescription in one year

* RTS = Returned to stock

Summary of literature

Before discussing the literature, a point must be clarified about terminology. When looking at the literature, the terms *prescription abandonment* and *primary non-adherence* overlap in studies that analyzed electronic prescriptions. With e-prescribing, it is difficult to differentiate between prescription abandonment and primary non-adherence because primary non-adherence will result eventually in prescription abandonment. However, prescription abandonment and primary non-adherence are two different terms. Primary non-adherence is related to newly initiated prescriptions, and prescription abandonment includes both new and old prescriptions. For electronic prescribing, however, the two terms end up being the same thing.

Filled prescriptions

Percentage of Abandoned Prescriptions

A study by Shrank et al (2010) evaluated the rate and predictors of abandoned prescriptions at a large national pharmacy chain (CVS) and a large national pharmacy benefit manager (Caremark).[15] The study outcome measures which are important for modeling medication waste are the rate at which prescriptions are filled, rate of abandoning a prescription with return to stock, and rate of abandoning a prescription with return to stock then purchasing it later. Authors estimated that the rate of prescription abandonment with return to stock was 3.27% with 1.5% of abandoned prescriptions re-purchased at a later date.

The study estimated an approximate cost of $5 per each abandoned prescription and concluded that the total annual cost of abandoned prescriptions at U.S. pharmacies

22

was more than $500 million. This total only reflected the cost of dispensing and did not consider other incurred costs such as the cost of a physician's visit or resource use associated with negative health outcomes. In addition, the reported abandonment rate only refers to retail pharmacies and may differ from rates at other outpatient pharmacies. A study by Bergeron et al (2013) investigated the rate of abandoning new prescriptions after implementation of electronic prescribing in one ambulatory care clinic.[16] Three patient cohorts were studied: 6 months before e-prescribing, 6 months after e-prescribing, and 12-18 months after e-prescribing. The prescription abandonment rate was 6.9% before e-prescribing; increasing to 10.6% after 6 months of e-prescribing, and stabilizing at 2.5% after 12-18 months. The final rate of 2.5% was comparable to 3.27% rate obtained by Shrank et al, but was limited to abandonment of newly initiated prescriptions.

Two other studies investigated the rate of prescription abandonment for newly initiated prescriptions. Streeter et al (2011) utilized data from a nationally representative pharmacy database to look at the effect of copayments on abandoning of newly initiated prescriptions for eight common oncolytic agents.[17] An abandoned prescription was defined as a prescription that is submitted to the pharmacy and has a reversed claim with no follow up claim. It was found that copayments were significantly associated with the prescription abandonment estimate of 10%. This rate was higher than other studies possibly due to the cost of the drugs and the study population.

Gleason et al (2009) examined the rate of abandoned prescriptions among newly initiated prescriptions for two sets of specialty drugs: TNF blocker therapy and MS therapy.[18] Data for the study came from a database from eight commercial health plans.

23

A trend analysis of the association between copayment and prescription abandonment rate found that prescription abandonment rate increased with copayments resulting in an abandonment rate of 4.7% to 26.4% for TNF blocker therapy and 5.7% to 28.5% for MS therapy.

In summary, the rate of abandonment of prescriptions in community settings ranged from 3.27% to 10% for most drugs. Abandonment of specialty medicines was much higher due to special circumstances associated with these drugs such as large co-payments.

Among the encountered studies in the literature review, only one attempted to estimate the cost of abandoned prescriptions. A single hospital outpatient pharmacy in Texas (1999) estimated its annual cost of abandoned prescriptions at more than $60,000 although this finding may not be externally valid to other settings.[18]

Unfilled prescriptions

There are two types of unfilled prescriptions. Unfilled prescriptions for newly initiated medications are called *primary non adherence.* Unfilled prescriptions for refills fall into the category of *secondary non-adherence* which is defined as filling a prescription but not taking it as prescribed.

Primary non-adherence

Four studies examined primary non-adherence in outpatient settings. Three examined primary non-adherence in prescription claims data and the fourth used a pharmacy database, allowing it to account for cash prescriptions.[20]

Fischer et al (2010) found that the rate of primary non-adherence in outpatient clinics with different specialties was 28.3%. Primary non-adherence was defined as rate at which patient did not fill new prescriptions.[21] Multivariate analysis showed that prescriptions of chronic diseases including antihypertensives, antidiabetics, and antihyperlipidemics were less likely to be filled compared to antimicrobial agents. This may suggest that patients are concerned with quick relief of symptoms rather than long term effects. In addition to primary non-adherence, the study estimated the rate of prescription non-fulfillment among all issued prescriptions to be 22.5%.

Jackson et al (2014) estimated that primary non-adherence in prescription medications of chronic conditions across 100 pharmacies was 12.2%.[20] This estimate used pharmacy dispensing data which accounted for cash and non-cash claims but only examined prescriptions for chronic diseases. Primary non-adherence was defined as a new electronic prescription for a patient aged 18 years and older that is not obtained within 30 days.

Raebel et al (2012) looked at primary non-adherence in an integrated healthcare system among three classes of medications: antidiabetic, antihypertensive, antihyperlipidemic and a fourth class of multiple medications use.[22] Primary non-adherence was defined as not picking up a new prescription medication within 30 days of order. The rate of primary non-adherence was significantly different between the three therapeutic groups: 7% for antihypertensives, 11% for antidiabetics, and 13% for antihyperlipidemics.

A study by Shin et al (2012) also used data from an integrated health system and found a similar estimate of primary non-adherence rate (9.8%) as Raebel et al.[90]

However, it examined primary non-adherence for drug classes used to treat both acute and chronic conditions.

In summary, definitions of primary non-adherence only varied slightly in the literature, and studies found that the rate of primary non-adherence varied between 7% and 28%. Lower percentages were reported in integrated health systems, where there is more focus to provide better services to patients. Higher percentages were reported from data drawn from populations which were not nationally representative. The estimate of primary non-adherence rate by Jackson et al (12.2%) was based on 100 retail pharmacies and considered the best estimate for the base case of the model.

Unfilled prescriptions

Three studies looked at unfilled prescriptions for both new and old prescriptions. The first study conducted by Kennedy et al (2008) addressed unfilled prescriptions among Medicare beneficiaries in community settings.[23] In the 2004 Medicare Current Beneficiary Survey (MCBS) Access to Care Survey, 4.6% of participants answered yes to the question "During the current year, were there any medicines prescribed for you that you did not get?" It was estimated that 4.4% (1.6 million) of all Medicare beneficiaries in the United States do not fill their prescriptions.

Fischer et al (2011) examined the rate of unfilled prescriptions by linking data from a national electronic prescribing system with claims data from a large national pharmacy benefit manager database.[91] Primary non-adherence was estimated as 24%, but including refill orders decreased the percentage of unfilled prescriptions to 14.5%.

The third study assessed self-reported prescription filling after an emergency department visit among Medicaid enrollees, comparing it to the pharmacy claims data as the gold standard.[24] According to patients, 90% of the prescriptions were filled (i.e. obtained by patients), but pharmacy claims data indicated that only 74% of the prescribed medications were filled. This indicates that self-report is not an accurate measure of prescription fulfillment.

Unfilled prescriptions

One study of patients not filling of handwritten prescriptions was conducted by Thomas et al (2006).[25] A telephone survey assessed primary non-adherence in a rural population to examine the effect of patient satisfaction with care and the quality of patient-physician relationship on patients' delay or failure to fill a prescription. The overall estimated rate of primary non-adherence based on patients' reports on unfilled prescriptions was 21.6% among study participants. This estimate may not be nationally representative because it was limited to rural areas where there are fewer pharmacies, difficulties in transportation, people with lower education levels and lower incomes.

Part 2: Literature review on unused prescription medications

The published literature on unused prescriptions covers a broad range of topics including quantifying the amount of unused prescription medications, storage and disposal practices at households, and possible consequences of unused prescription medications (water pollution, health impact, cost to healthcare system, non-medical use, medication sharing, and diversion). This literature review focused on quantifying unused prescription household medications and those returned to pharmacies. Studies associated with unused prescription medications in institutional settings like hospital in-

patient and nursing homes care were not considered. Search terms used are summarized in Table 2.3 and the literature search is summarized in Figure 2.2. Titles and abstracts of articles were checked for inclusion and exclusion criteria. The overall search revealed 474 articles. References from the included articles were also reviewed for additional relevant articles. After applying inclusion and exclusion criteria and eliminating duplicates, 13 unique eligible articles were found.[92-104] Of these, 6 articles were selected for discussion (Table 2.4), because they were the most recent, were more generalizable to national settings, and addressed costs as well as quantifying the amount of unused prescription medications.

Table 2.3. Search terms history for unused prescription medications

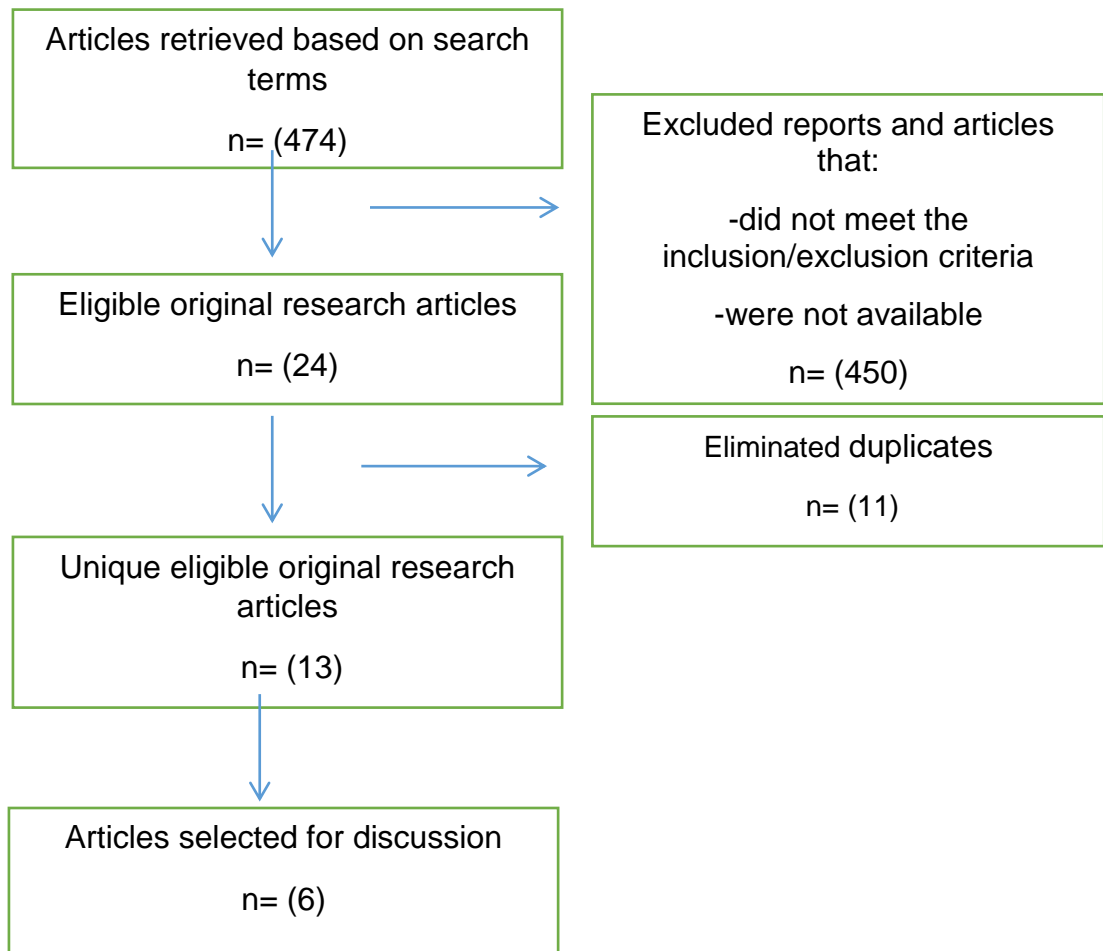| Search term	Eligible articles			Total
	PubMed	IPA	CINHAL	
Unused prescription medications	1	6	1	
Unused medications	2	8	4	
Wasted medications	1	1	-	
Unique eligible articles				13

Figure 2.2 Flow chart summary of literature search

The literature revealed limited research about unused prescription medications in outpatient settings. The articles can be divided in to two parts: unused prescription medications in households and unused prescription medications returned to a pharmacy or medication take back event.

Table 2.4 Summary of included articles of unused prescription medications

Author	Study design and sample	Sample size	Outcome measure of interest to our model	Setting and data source	Findings relating to our research
Wieczorkiewicz et al 2013	- Phone survey - Adults ≥ 18 years old	445 surveys	To determine households'' use, store, and dispose of medications	- Patients were phone interviewed	- Average number of prescription medications was 4.4 - 30% of respondents do not use their prescription medications regularly - 23% have expired prescription medications
Lewis et al 2014	- Survey (face to face interviews) - US veterans	191 participants	Investigate use and disposal of prescription opioids	- Veterans Affairs Palo Alto Health Care System (VAPAHCS) - Electronic medical records - Patients' interviews	- 65.4% of patients store unused prescription opioids - Only one third of patients used all prescribed opioids or discarded unused
Bates et al 2011	- phone and mail survey - Adult patients who underwent urological surgery	275 participant	- Patients' satisfaction with pain - use and disposal of narcotics	- Chart review - Phone interview - Patient administered questionnaire	- 67% of patients have leftover medications - 90.8% of patients stored leftover medications
Morgan TM	- Cross sectional	73	- Assessed	- One retirement	- Total cost of wasted

2001	survey - Elderly residents age ≥ 65 years old	participant	prescription medications use	community - Patients home interview - Pill sort at patients' homes	medications = $2011 - Average annual cost per person = $30.47 (2.3% of the total annual costs per person)
Perry et al 2014	- Prescription medications take back event - Patients' survey	818 surveys	- Quantify medication waste, cost, and assess disposal practices	- One local community - Event held for 7 days - Patient's administered survey	- More than 780 thousand wasted dosing units with a total cost of more than $1 million
Garey et al 2004	- Community campaign - Patients returning prescription and over the counter medications	-	- Investigate quantity, cost, and types of returned medications	- One community pharmacy	- 1315 medication containers were returned - 65% of returned medications were prescription medications - Total cost of returned medications = $26,222

Unused prescription medications in households

Four studies assessed the non-use of prescription medications among adult population (aged 18 years and above). Three of the four studies used phone or mail surveys to collect data, [92,93,94] and the fourth used both patient surveys and a home visit.[95]

Wieczorkiewicz et al (2013) investigated unused medications (prescription and non-prescription) in households in Cook County, Illinois.[92] A phone survey revealed that about one third of patients did not use their medications regularly and expired prescription medications accumulated in 23% of the study participants. The monetary cost was not quantified.

Lewis et al (2014) investigated unused prescription opioids among a veteran population.[93] Stockpiling of unused opioids was reported by 65% with only 6.3% of patients disposing of unused opioids. Stockpiling opioids was associated with recreational use of these medications in 34% of patients. A similar study by Bates et al (2011) investigated unused narcotics among discharged patients who underwent surgery.[94] In this study, 67% of patients stockpiled unused narcotics.

Combining home visits with questionnaires, Morgan (2001) found that 52% of patients in a retirement community wasted 2078 doses of prescription medications (i.e. medicines kept with no intention to use).[95] The total cost of waste was $2011 for the study group and the average annual cost of wasted prescriptions per participant was estimated at $30.47. The study looked at both the amount and the cost of wasted prescription medications, but did not examine wasted physician or pharmacist time.

A news release in 2006 showed results of a national prescription drug survey conducted by The National Community Pharmacists Association (NCPA) in collaboration with Pharmacists for the Protection of Patient Care (P3C) group; the survey revealed that 49% of patients forgot to take at least some of their prescribed medications and 24% took less than the prescribed doses.[96]

Unused prescription medications returned to a pharmacy or a medication take back event

Several studies examined medications collected in take back events.[97,98,99,100] These studies quantified the amount of unused or expired medications collected, estimated their associated cost, and surveyed patients about reasons behind non-use. Perry et al (2014) described 7 prescription medication take back events that were held in a local community in Ohio.[101] This study was the largest of its kind and included all dosage forms when estimating cost. 800,000 dosing units were collected over 7 days with an estimated average wholesale cost of more than $1 million.

A study of dropped-off unused medications by Garey et al (2004) in Houston, Texas found that the majority (65%) of unused medications were prescription medications.[102] The estimated cost of all unused medications returned to the pharmacy was more than $26,000.

A newly published study (2014) investigated unused medications at households in a local community.[103] In phase 1 of the study, a web survey was conducted; the results showed that the ratio of unused to used medications was 2:3 with an estimated cost of unused medications at more than $23,000. In the second phase, a paper based survey among patients who returned unused medications to community pharmacies was

conducted. A total of 776 unused medications where returned for disposal at an estimated cost of more than $59,000. The total cost of unused medications among adults was extrapolated to be $117.5 billion on the national level.

Overview of the literature

Studies of unfilled, abandoned prescriptions, and unused prescription medications can allow a model of medication waste to be developed. Only some of the data in the literature is nationally representative but assumptions and sensitivity analyses can be used to deal with sources of variability in the data. Using estimates of waste in the literature, costs can be assigned to estimate the total direct costs associated with wastage in delivery of care attributed to medication waste.

Chapter 3

Methods

Study design

A cost of illness model was developed using data from the literature, and a retrospective cross sectional study of the Medical Expenditure Panel Survey (MEPS) 2012 was conducted. The MEPS is a nationally representative database of the civilian, noninstitutionalized population of the United States. In the model, direct medical costs of medication waste (exclusive of impact on health outcomes) were investigated. Indirect and intangible costs are not considered. Direct medical costs of unfilled, abandoned prescriptions, and unused prescription medications were estimated over a one year period using a bottom up approach. All cost estimates were converted to 2014 values by applying yearly healthcare inflation rates. Prevalence estimates of unfilled, abandoned prescriptions, and unused prescription medications for U.S. population were considered in the current study.

Economic model:

Direct medical costs associated with wastage in delivery of care due to medication waste are illustrated in Figure1.1 (repeated here for convenience of the reader).
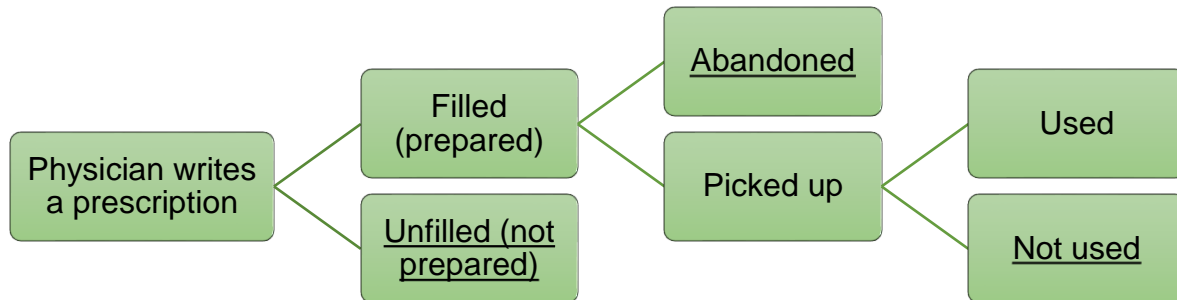
35

Figure1.1 Model of the medication use process: underlined words represent points where direct medical costs are incurred.

Points at which prescription medication waste is identified are:

1. Not filling a prescription (Cost of physician time writing a prescription)

2. Abandoning a prescription (Cost of physician time writing a prescription and a pharmacist's time preparing the prescription)

3. Picking up a prescription, but not using the prescribed medications (Cost of physician time writing a prescription, a pharmacist's time preparing the prescription, and the cost of the medications dispensed but not used as directed)

Model assumptions

The model was built on the following assumptions:

1. 100% of prescriptions transmitted electronically or via fax or phone were by pharmacists without any action from the patient.

2. For handwritten prescriptions, only those hand-delivered to the pharmacy were filled by the pharmacist

3. The rate of unfilled prescriptions was the same as rate of abandoned prescriptions based on the fact that abandoning a prescription and not delivering a handwritten prescription to the pharmacy are two separate consequences of patient's intention to not fill (obtain) the prescription. The difference between the two is the nature of the transmittal process of the prescription (i.e. electronic, fax, phone or hand-delivery)

4. A prescription was considered abandoned after two weeks of delivery to the pharmacy.

5. Every abandoned prescription was returned to stock

6. Prescriptions with automatic refills were excluded from the model

7. Unused prescription medications were a result of patients' non-adherence to drug therapy (i.e. patients do not consume the entire quantity prescribed, leading to unused leftover medications).

8. A one year period was the time frame of the study

9. The rate of unfilled, abandoned, and unused prescriptions was considered constant throughout the study period.

Data sources

Prescription data

The total number of prescriptions written in outpatient settings for the year 2012 was obtained using steps 1 and 2 below:

1. The total number of office based visits, outpatient visits, and emergency room visits involving written prescriptions was drawn using the variable (MEDPRESC)

in the three MEPS data files: Office-Based Medical Provider Visits, Outpatient

Visits, and Emergency Room Visits files

2. The total number of prescriptions written in outpatient settings was obtained by

multiplying the total number of all visits involving written prescriptions (in step 1)

by the average number of prescriptions per visit. The National Ambulatory

Medical Care Survey (NAMCS) and The National Hospital Ambulatory Medical

Care Survey (NHAMCS) were used to calculate the average number of

prescriptions written per office based visit, hospital outpatient visit, and

emergency room visit.[104,105,106]

In 2012, the total number of office based visits, hospital outpatient visits, and

emergency room visits that involved written prescriptions reported in MEPS was

277,226,561 visits. According to NAMCS and NHAMCS, the average number of drug

mentions in one visit varied between 3.4 for office-based visits (2010)[104], 3.6 for hospital

outpatient visits (2011) and 2.6 for emergency room visits (2011).[105,106] In our base case

model, we assumed the average number of prescriptions written in a single visit at a

conservative total of three. This was done to take into account the fact that some office

based visits include prescriptions for medications that are not self- administered by

patients such as immunizations and other injectables. When the average number of 3

was multiplied by the total number of outpatient visits involving written prescriptions for

the year 2012 (277,226,561), we ended up with a total of 831,679,683 prescriptions per

year. This number was multiplied by the assumed rates of unfilled prescriptions,

abandoned prescriptions, and prescriptions dispensed but not used to get their

respective totals.

Prevalence estimates

The rate of abandoned prescriptions use in the model was based on the Shrank et al study (2010) which investigated the rate of prescription abandonment in a large chain community pharmacy.[15] This study was chosen because it examined abandonment of new and refill prescriptions as well as prescriptions delivered electronically or by hand. It also used data from a large national pharmacy chain and a large national pharmacy benefit manager, providing a rate of abandoned prescriptions that should be nationally representative.

The average rate of prescription medications dispensed but not used as directed was obtained from Claxton et al (2001)[107].This paper was a systematic review which assessed adherence using electronic monitoring devices. Patients' adherence was assessed by looking at whether the appropriate number of doses were taken during each day or not. The study reported an average rate of adherence of four dose regimens across a variety of therapeutic classes. Although the review was in 2001, it was the only encountered study that provided an average rate of unused acute and chronic medications. The average rate of non-adherence was 29%.

Cost data

Costs of office-based physicians' visits and other outpatient visits came from Medicare reimbursement costs for physicians' fees obtained by using Current Procedural Terminology (CPT) codes. CPT codes were used to identify physicians' visits involving an order for a prescription, however, no specific CPT codes were available for such visits. So, CPT codes used were: 99203 (a physician visit for a

condition of low to moderate patient severity level and a medical decision of low complexity for new patients) and 99213 (a physician visit of low to moderate patient severity level and a medical decision of low complexity for established patients).[108] CPT codes for non-facility based visits were used because most of prescriptions are generated during office based visits. Average reimbursement of the two codes was used in the model.

Average dispensing cost was based on a national study which estimated the national average cost of dispensing per prescription incurred by community retail pharmacies.[109] Cost of dispensing incorporated direct costs, salary expenses, and overhead costs.[109,110]

The average prescription cost was obtained from MEPS using the variable (RXXP12X) from the prescribed medicines file (2012), which represents the mean total payments (from 12 sources of payments) per each purchased prescription.

Cost calculation

Overall cost of medication waste

A prevalence based method was used to estimate the economic burden of medication waste. In this method, the prevalence of wasted prescriptions (either unfilled, abandoned, or unused prescription) during a specific time period (one year) was measured and assigned a cost using a bottom up approach. In this approach, the mean cost per unit is calculated and multiplied by the total number of units. Total costs for unfilled, abandoned, and unused prescription were summed together to obtain the overall cost.

Specific objective 1:

To estimate the annual direct medical costs of medication waste in delivery of care with regard to unfilled and abandoned prescriptions. The variables considered for estimating the direct medical costs per an unfilled and abandoned prescription are listed in Table 3.1.

Table 3.1 Cost variables of unfilled and abandoned prescriptions

Cost variable	Costs associated with unfilled prescriptions	Costs associated with abandoned prescriptions
Mean cost of office based physicians' visits and other outpatient visits^	*	*
Mean dispensing cost		*

^Mean cost of office based physician's visit and other outpatient visits is computed based on Medicare reimbursement of physicians' fees. An average of the average cost of both new and established patients' visits is calculated and used. Reimbursement for other components of physicians' visits like diagnostic procedures, laboratory services and prescribed medications are not considered as they don't fit to the cost of unfilled and abandoned prescriptions.

Specific objective2:

To estimate the annual direct medical costs of medication waste in delivery of care with regard to unused prescription medications. The variables considered in estimating the direct medical costs per an unused prescription are:

- Mean cost of office based physician's visit and other outpatient visits

- Mean prescription cost

Data analysis

Data were analyzed by decision analysis performed using the TreeAge software, Inc. v14 for Healthcare. A decision tree was built (see Figure 3.1) mapping out the possible outcomes of writing a prescription by a physician and assigning probabilities that unfilled, abandoned, and unused prescription medications will occur as well as its average cost (in dollars). A folding back technique was used to estimate the expected value (weighted average cost) per wasted prescription (either unfilled, abandoned, or unused prescription). This technique works by multiplying the probability that each outcome will occur by its cost and it starts from the right side of the decision tree (Figure 3.1) and works leftward. Mean cost per unfilled, abandoned, and unused prescription was also provided at terminal nodes (indicated by triangles at the end of the tree).
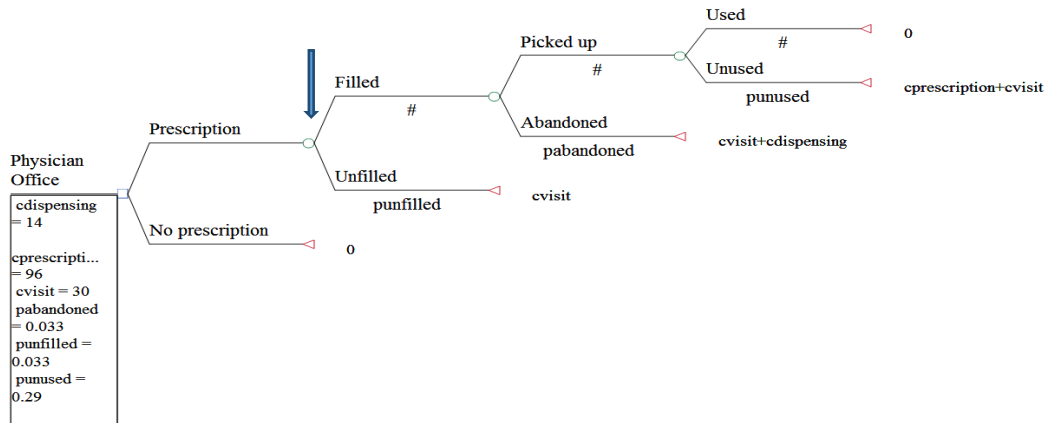

Figure 3.1 Decision tree analysis: outcomes that don't represent medication waste are assigned zero values; arrow represents point where average weighted cost per prescription is estimated

Sensitivity analyses

One way sensitivity analysis and probabilistic sensitivity analysis (PSA) were performed using the TreeAge software. The aim of these sensitivity analyses was to test the robustness of the estimated average cost of medication waste. This is due to uncertainties in the selected parameter estimates such as cost or probabilities of events. A tornado diagram was made to illustrate the sensitivity of the estimated cost to the variables used in the model.

In one way sensitivity analysis, the value of one variable is varied in the model while keeping values of other variables constant. To determine variable ranges used in the sensitivity analysis, 95% confidence interval limits were used when possible. When no confidence intervals or standard deviations were reported, the highest and lowest value estimates reported in the literature were used. When neither of these options were available, averages for variables were increased and decreased by 20%.

For unused prescription medications, Claxton et al provided a wide range of values (from 3% to 66%). This was considered too wide for a sensitivity analysis, so a ±20% range was used.

The rate of abandoned prescriptions also had a wide range in the literature (from 3.27% to 28.3%). The upper range reported by Fischer et al (2010) was not used because it was not nationally representative. Therefore, the rate of 14.5% reported by Fischer et al (2011) was used as the upper limit for abandoned prescription rate.

The average prescription cost was reported in MEPS along with the standard error, so a 95% confidence interval was used as the range for the sensitivity analysis. The

43

average cost of physician's based office visit and other outpatient visits was varied between zero and the base case value. Average dispensing cost, average number of prescriptions written per visit and total number of visits involving written prescriptions were varied over ±20% range.

In PSA, the combined uncertainty of all variables included in the model was tested using Monte Carlo simulation. Each parameter estimate (for example mean dispensing cost) was assigned a probability distribution and the software randomly picked a value for each estimate (for all estimates at the same time) from its distribution to calculate the mean cost of waste prescription. This process was repeated many times to calculate a distribution probability for costs of medication waste. In our model, beta distribution was assigned for outcomes' probabilities and gamma distribution for cost variables. Beta distribution limits the output to values between 0 and 1 making it suitable for probability outcomes. Gamma distribution is recommended for modeling non-negative data such as cost. When assigning distributions, the mean was set to be equal to the base line value and the standard deviation was calculated based on the following formula: Upper limit – lower limit / (2X1.96).[111]

The process of running the model was repeated with different combinations of parameter estimates at each time providing the mean of the expected value of the cost of a wasted prescription. Table 3.2 lists the baseline values and ranges for all variables included in one way sensitivity analyses and the distributions assigned to each variable in probabilistic sensitivity analysis.

Table 3.2 Key variables and ranges used in one way sensitivity analysis

Variable	Baseline	Source	Range	Source	Distribution assigned for PSA
Mean office based physician's visit and other outpatient visits cost*	$30**	CPT (2014)	($0 – $30)**	***	Gamma
Mean dispensing cost	$14	National cost of dispensing study (2007)	($11 – $17)**	***	Gamma
Mean prescription cost	$96	MEPS (2012)	($90 – $102)**	MEPS	Gamma
Probability of abandoned prescriptions	0.033	Shrank et al (2010)	(0.026 - 0.04)	*** Fischer et al (2011)	Beta
Probability of unused prescriptions	0.29	Claxton et al (2001)	(0.232 – 0.348)	***	Beta
Probability of unfilled prescriptions	0.033	-	(0.026 - 0.04)	***	Beta
Average number of prescriptions written per visit	3	NAMCS /NHAMCS	(2.4 – 3.6)	***	-
Total number of visits involving written prescriptions	277,226,561	MEPS	(221,781,249 - 332,671,873)**	***	-

*(Average cost of office based and other outpatient visits for new patient + average cost of office based and other outpatient visits for established patient) divided by 2: (106.1 + 71.81)/2 =

88.955; however, $29.7 was used in the model based on the assumption that three prescriptions are written per visit
**Rounded to the nearest whole number
*** ±20% was used due to lack of data

Chapter 4

Results

Base case analysis

An estimated 831,679,683 prescriptions were written in outpatient settings in 2012. The total number of unfilled, abandoned, and unused prescriptions is summarized in Table 4.1. Data were analyzed by decision analysis modeling and the base case results are shown in Figure 4.1. The weighted average cost per wasted prescription (either unfilled, abandoned, or unused prescription) is $37; mean cost per unfilled, abandoned, and unused prescription is $30, $44, and $126, respectively. The total annual direct medical costs associated with wastage in delivery of care attributed to medication waste is estimated at $30.4 billion. Table 4.2 shows a breakdown of overall cost by waste component; unused prescription medications contribute to more than 93% of the overall cost.

47

Table 4.1. Total number of unfilled, abandoned, and unused prescriptions

	Method of calculation	Total number of prescriptions
Unfilled prescriptions	0.033* X total no. of written prescriptions (831,679,683***)	27,445430
Abandoned prescriptions	0.033* X total no. of filled prescriptions (804,234,253****)	26,539,730
Unused prescriptions	0.29** X total no. of picked up prescriptions (777,694,523*****)	225,531,412

*Shrank et al (2010)

** Claxton et al (2001)

***Total number of physician visits (MEPS 2012) times 3 prescriptions per visit

****Total number of written prescriptions times rate of filled prescriptions (0.967)

*****Total number of filled prescriptions – total number of abandoned prescriptions
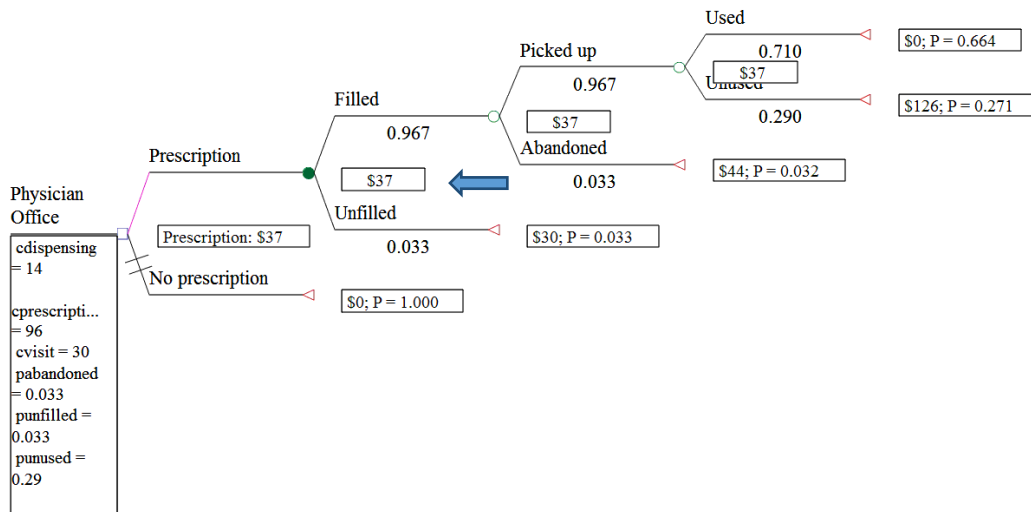
Figure 4.1 Base case results using decision analysis modeling. The arrow indicates the weighted average cost per a wasted prescription.

Table 4.2. Overall cost by unfilled, abandoned and unused prescriptions*

Cost component	No. of occurrences in one year**	Mean cost per event	Annual direct medical costs (in millions)**
Unfilled prescriptions	27,445,430	$30	$823
Abandoned prescriptions	26,539,730	$44	$1,168
Unused prescriptions	225,531,412	$126	$28,417.0
Total annual direct medical costs			**$30,408**

*All costs are in US dollars 2014 values
**Rounded to the nearest whole number

Table 4.3 Total direct medical costs by type of visit

	Office based visits	Hospital outpatient visits	Emergency room visits
Number of visits involving written prescriptions	244,286,605	12,433,294	20,506,662
Number of prescriptions*	732,859,815	37,299,882	61,519,986
Annual direct medical costs (in millions)	$27,116	$1,380	$2,276
Share of the total cost*	89.2%	4.5%	7.5%

*No. of prescriptions = No. of visits involving written prescriptions X 3
**Rounded to the nearest whole number
***Numbers may not add to 100 due to rounding
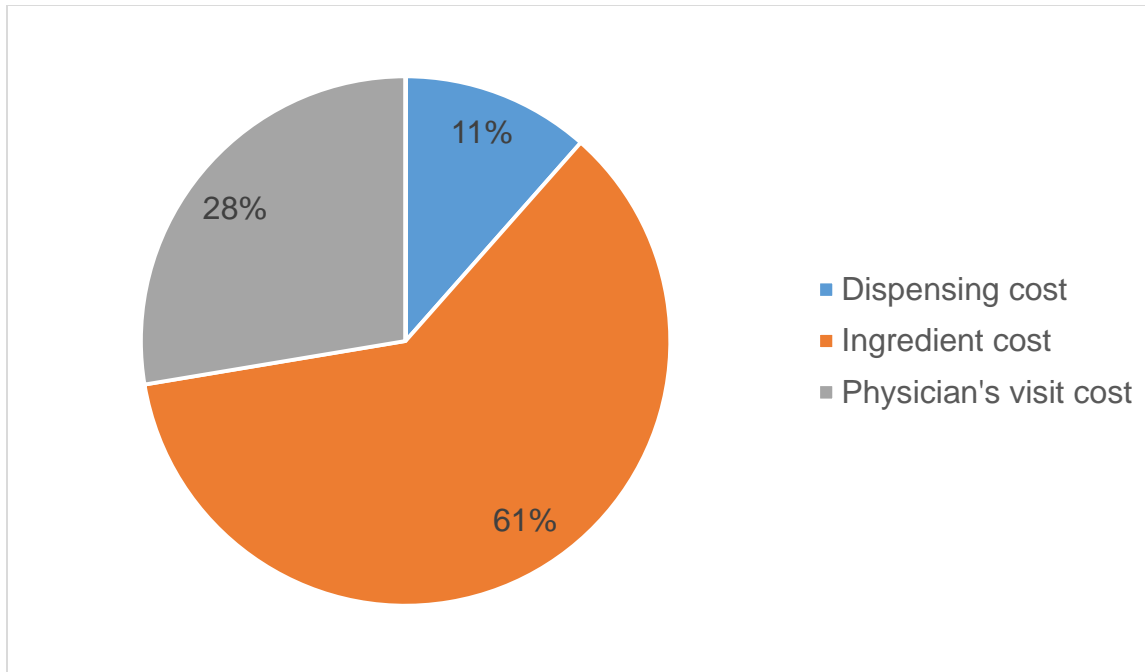
Figure 4.2 Share of dispensing cost and ingredient cost to overall cost

The total estimated cost is also presented in terms of type of outpatient visit. The share of office based visits, hospital outpatient visits, and emergency room visits to overall cost is shown in Table 4.3. Prescriptions written in physician's office account for most of the waste with an estimated cost of $27 billion.

The share of dispensing cost and ingredient cost was also calculated. The total average dispensing cost incurred by abandoned prescriptions and unused prescription medications was estimated at $3.5 billion, which represents 11.5% of the overall cost. The estimated average ingredient cost per prescription estimated was $82 and the total average ingredient cost was $18.5 billion, which represents almost 61% of the total estimated cost. Figure 4.2 shows the share of dispensing cost, ingredient cost, physician's visit cost to overall cost.

Sensitivity analyses

One way sensitivity analysis

A Tornado diagram illustrated one way sensitivity analyses for all variables in the model (Figure 4.3). Overall cost was most sensitive to the average rate of unused prescription medications, costs per office based visits, and cost of the medications prescribed. Varying the probability of unused medications over ±20% range resulted in approximately ± $5.4 billion effect on overall estimated cost. When the mean office based visit cost varied between ($0 and $30), the total cost ranged from $21.6 billion to $30.8 billion. Mean prescription costs had an effect of ± $1.3 billion on the overall estimated cost. Mean dispensing costs, probability of medications being abandoned, and probability of prescriptions not being filled had little effect on overall costs of medication waste (Table 4.4).

Probabilistic sensitivity analysis (Monte Carlo simulation)

A probabilistic sensitivity analysis (PSA) was conducted using all the variables in the model. A Monte Carlo simulation was run for 10 thousand iterations giving an average expected cost per wasted prescription of $37 (95%CI: $27 – $47) and thus, an overall cost of $30.4 billion (95% CI: $22.5 billion – $39.1 billion). Results of Monte Carlo simulation are summarized in Table 4.5.

51

Tornado Sensitivity Analysis

Legend:
- punused (0.232 to 0.348)
- evisit (0.0 to 30.0)
- eprescription (90.0 to 102.0)
- edispensing (11.0 to 17.0)
- pabandoned (0.026 to 0.04)
- punfilled (0.026 to 0.04)

36.562

EV: 36.6
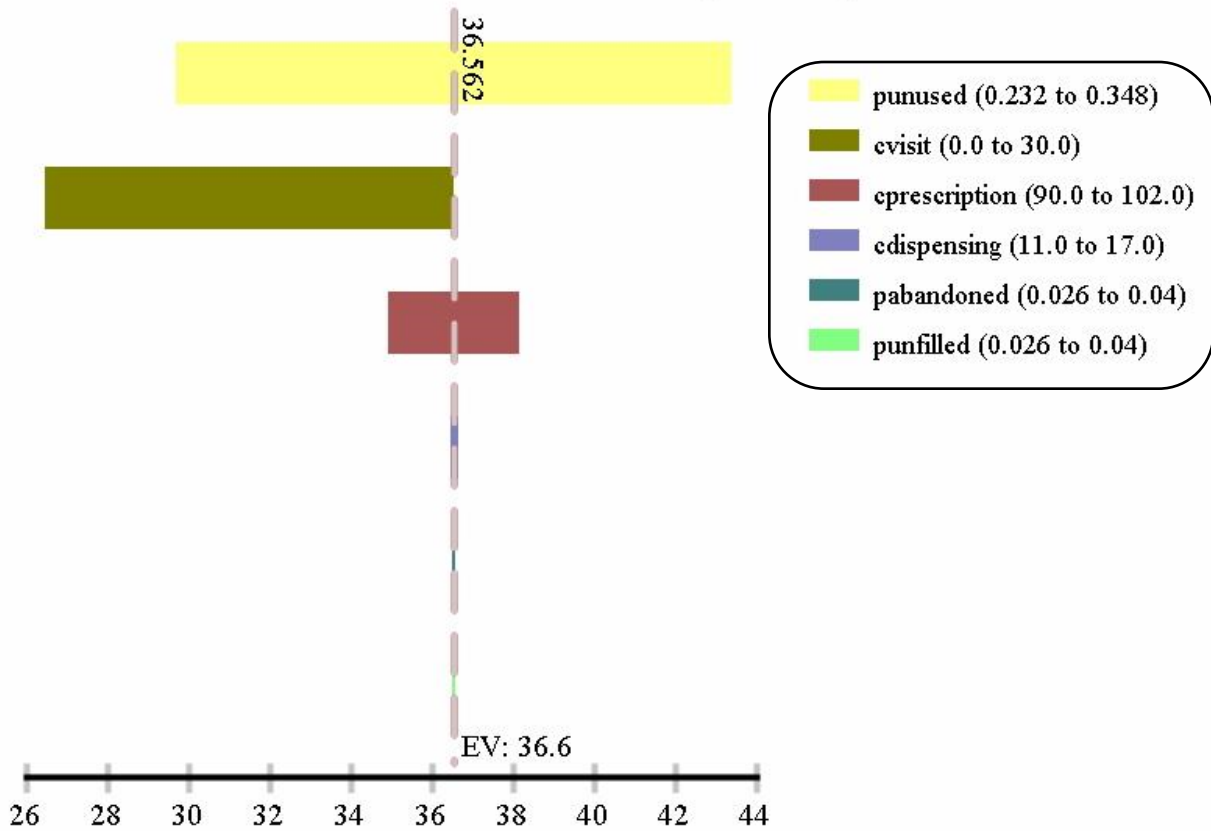
Figure 4.4 One way sensitivity analysis on all variables: box represent range of values used in sensitivity analysis for each variable.

Table 4.4 Results of one way sensitivity analyses (USD 2014 values)*

Variable	Range	Average cost per wasted prescription	Total annual direct medical costs** (in millions)
Mean office based physician's visit and other outpatient visits cost	($0 - $30)	($26 - $37)	($21,624 – $30,772)
Mean dispensing cost	($11 – $17)	($36 – $37)	($29,940 – $30,772)
Mean prescription cost	($90– $102)	($35 - $38)	($29,109 – $31,604)
Probability of abandoned prescriptions	(0.026 - 0.04)	($37***)	($30,772)
Probability of unused prescriptions	(0.232 – 0.348)	($30 – 443)	($24,950 – $35,762)
Probability of unfilled prescriptions	(0.026 - 0.04)	($37***)	($30,772)
Average no. of prescriptions written per visit	(2.4 – 3.6)	-	($24,618 – $36,927)
Number of visits involving written prescriptions**	(221,781,249 - 332,671,873)	-	($24,618 – $36,927)

*USD: US dollars

** Rounded to the nearest whole number

***Varying the probability over the range (0.026 – 0.04) yields an average cost of wasted prescription of $37

Table 4.5 Results of probabilistic sensitivity analysis (USD 2014 values)*

After 10,000 simulations	Expected cost per wasted prescription
Mean	$37
Median	$36
SD	$5
Minimum	$22
Maximum	$58

*USD: US dollars.

Chapter 5

Section 5.1: Discussion

This study examines medication waste associated with the medication use process. It quantifies the costs of medication waste in the United States exclusive of impact on health outcomes. It is unique in its exploration of the waste associated with wasted health care inputs including physician time spent diagnosing and prescribing for medications the patient does not use or uses inappropriately, time spent by pharmacists who fill prescriptions that are not picked up or taken incorrectly, and costs of medications which are dispensed but not taken as directed.

In this research, a model was developed which used a unique definition of medication waste. Other studies defined waste related to impact on health outcomes or environmental effects. This study defined medication waste in terms of waste in prescribing, dispensing, and non-consumption of medications. Therefore costs estimated in the study were specific to waste in delivery of care due to unfilled, abandoned, and unused prescription medications. Wastage in delivery of care means that healthcare personnel squander their time and efforts in activities that don't result in any meaningful benefit to patients. In this study, the total estimated costs associated with such waste was $30.4 billion (95% CI: $22.5 billion – $39.1 billion). This sum

excludes costs related to hospitalizations, physician visits, nursing home admissions, emergency department visits, and any additional resources used because of medication waste.

Unused prescription medications contributed most to the overall cost of medication waste. Figure 5.1 illustrates the relative impact of each component on overall medication waste. Unused prescription medications accounted for most of the waste with a total cost of more than $28 billion. Improving medication adherence in patients can reduce this waste significantly.

Figure 5.1 Relative impact of each component on overall medication waste
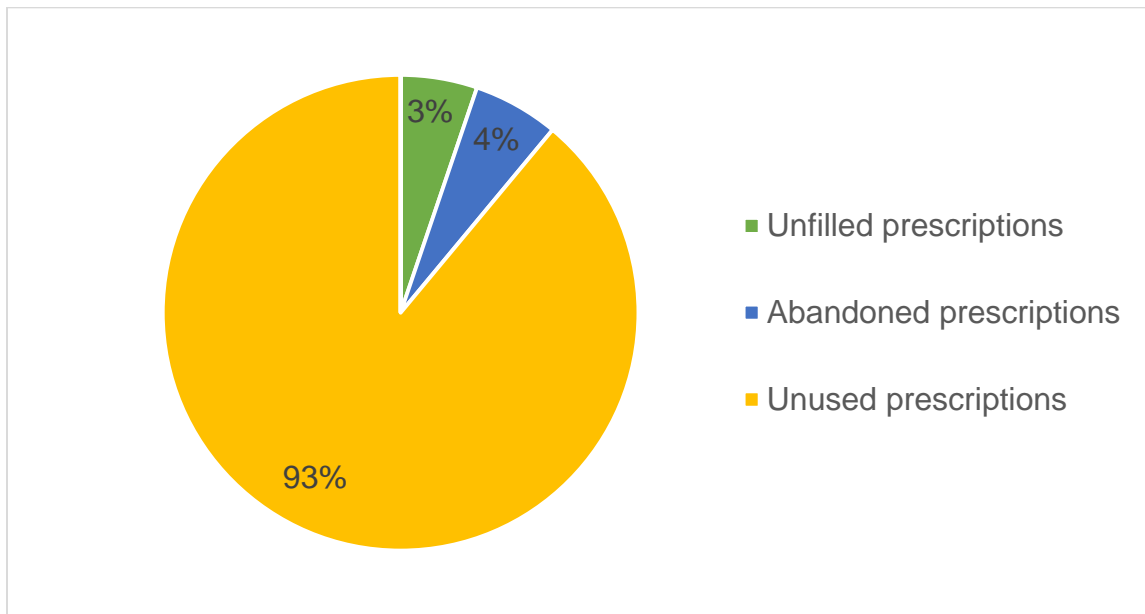
Compared to other studies that examined unused medications, this study used a novel approach. Other studies only included the ingredient cost of medications and use the Average Wholesale Price (AWP) to estimate the cost of unused medications.[95,100,101,102] In contrast, we incorporated costs of dispensing and physician's

الم‍ـنـارة للاستشارات

www.manaraa.com

visits as components of the overall cost of unused prescription medications. This captured waste in the medication use system that was ignored in previous research.

In addition, the data used for estimating the cost of wasted prescriptions was collected from nationally representative sources, something which most other encountered studies failed to do. Only two other studies attempted to quantify costs nationally. One used a single community pharmacy to extrapolate their findings nationwide.[103] The other used a convenience sample of 73 New Hampshire retirement community residents to come up with an estimate of medication waste in senior populations.[95] The causes behind medication waste are complex and varied. Individual characteristics of patients like physical impairments, cognitive problems, and age-related concerns may prevent them from filling, picking up, or taking prescription medications as directed. The patient's medical condition (e.g., depression) may also get in the way. Structural barriers in the US Health Care System like inadequate continuity of care or poor provider–patient communications can prevent appropriate medication use. In addition, the complexity of therapeutic regimens, adverse effects associated with medication, and socioeconomic causes can reduce effective medication use.

Because of the complexity of causes behind medication waste, the solution will require diverse strategies that increase patient engagement and participation in their care. Reducing medication waste requires patients to fill, pick up, and take their medications. Health care providers like physicians and pharmacists can make the process easier, but patients must do their job too.

Improving relationships between patients and their providers, both physicians and pharmacists combined with systems that address the barriers to appropriate patient

57

behaviors can help reduce prescription drug waste. Innovations like appointment based medication synchronization can reduce medication waste.

Appointment based medication synchronization (ABMS) can reduce waste by allowing patients to meet with their pharmacists to solve medication-related problems and synchronize prescriptions to be dispensed on a single day of the month.[112] Significant improvement in medication adherence has been demonstrated with ABMS. Better adherence with ABMS may also be associated with less waste.

ABMS blends technology with face-to-face contact with pharmacists to address the causes of non-adherence and medication waste. It allows pharmacists to proactively manage patients' medication-related needs. ABMS provides the pharmacist an opportunity to engage in mutual problem solving with the patient about their medications and it can help resolve issues like simple forgetfulness, poor continuity of care, poor provider–patient communications, and insurance glitches.

Our definition of medication waste is unique. A study of medication waste conducted by the IMS institute published in 2013 estimated that $213 billion are wasted due to suboptimal use of medications.[6] Waste was defined in terms of six areas listed in Table 5.1. Medication non-adherence (primary and secondary) accounted for 50% of the total waste. For each area, costs were calculated based on increased utilization of four sites of care: hospitalizations, outpatient visits, pharmacy, and emergency room visits, which occurred as consequences of the suboptimal use of medications. Pharmacy utilization accounted for $22 billion (10%) of the total estimated cost; this is because more prescriptions are issued to patients with deteriorated health conditions as a result of medication non-adherence.

58

Our study differs from the IMS study in the definition of medication waste and the related costs. Table 5.2 compared the different components considered by both studies.

This study has a number of limitations. The first was related to the specific types of costs we captured. We only looked at direct medical costs associated with wastage in delivery of care. There are other direct medical and non-medical costs as well as indirect costs that are related to the problem. These unaddressed costs include cost of impact on health outcomes, which may result from worsening health conditions; cost of impact on environment as a consequence of water and soil pollution; and cost of implementing strategies to overcome the problem such as medication take back events. Thus, our estimate of $30.4 billion represents only a small portion of the economic burden of medication waste, which may be addressed in future research.

Another limitation is that we were not able to determine what percentage of all dispensed medications are not used. We only captured the percentage of unused medications due to secondary non-adherence. This is because we obtained the rate of unused medications from a previous study that evaluated medication non-adherence. There is an undetermined percentage of unused medications caused by other factors such as treatment resistance, overprescribing, patients' death, and others.

Another limitation is the variability in our sources. Our data came from many sources -- some published and other from secondary databases. The challenge was to link the data from different resources and make them compatible. Also, some assumptions were made about variables because data was not available. We attempted to address issues of variability and compatibility in the sensitivity analyses.

59

When conducting the study, our intention was to focus on patient's role in leading to medication waste, more specifically, patients' actions or non-actions in the medication use process. However, this was not necessarily met when we looked at unfilled and abandoned prescriptions. Patient's intention to not fill or abandon a prescription could not be captured through the literature. In other words, such actions could happen as a consequence of other factors rather than patient's intention to not use the prescribed medicine. These factors include the availability of medicine at home, physician's instructions to not fill the prescription until the symptoms last for a number of days, or it could be the payer who refuses the prescription.

Also, it is possible that we overestimated the overall cost because we used physician's visit costs as one of the costs associated with unfilled, abandoned, and unused prescriptions. However, there is still an economic value in the physician's visit beyond writing a prescription. When physician's visit cost was eliminated from the model in the sensitivity analysis, the overall estimated cost dropped by almost $9 billion, which constitutes approximately one third of the overall estimated cost.

Finally, there is limited generalizability of our results. We used data based on community pharmacies only and thus, it may not be applicable to other outpatient pharmacies.

Table 5.1 Areas of suboptimal use of medications and associated costs based on IMS study[6]

Area	Cost (In billion)
Medication non-adherence	$105.4
Delayed evidence based treatment practice	$39.5
Antibiotic misuse	$35.1
Medication errors	$20.0
Suboptimal generics use	$11.9
Mismanaged polypharmacy in the elderly	$1.3
Total cost	$213.2

Table 5.2 Comparison between the current study and the IMS study

	Type of waste	Associated cost (in billion)	Total estimated cost (in billion)
Current study	Unfilled prescriptions Abandoned prescriptions Unused prescription medications	$0.8 $1.2 $28.4	**$30.4**
IMS study[6]	Hospital admissions Outpatient visits Prescriptions Emergency room visits	$140 $45 $22 $6	**$213**

Section 5.2: Conclusion

Medication waste associated with unfilled, abandoned, and unused prescription medications is a significant burden on the US Healthcare System. Medication use process starts when a physician writes a medication prescription and ends by patients using or not using their dispensed medications. Patients who don't fulfill their role in the medication use process cause a considerable amount of monetary wastage estimated in our study at $30.4 billion. Instead of being wasted, money spent on these avoidable costs could be used to treat a large number of patients.

There are different reasons that lead to medication waste; patients' medication non-adherence is the primary leader to such a problem. To reduce the intensity of medication waste, healthcare policy makers should focus on stablishing plans that help increase patient engagement in their care.

Section 5.3: Study implications

This study estimated the overall cost of medication waste considering only wastage inputs. Future studies that address medication waste considering other direct and indirect costs are needed to provide a more comprehensive estimate of the overall cost.

Our study is limited to waste in the United States healthcare system. Efforts should be increased to reduce waste in the US and worldwide.

List of References

List of References

1. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (December 28, 2010). The DAWN Report: Highlights of the 2009 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits. Rockville, MD.

2. Prevent Unintentional Poisoning. United States: Center for Disease Control and Prevention, National Center for Injury Prevention and Control; 2012. Available from: http://www.cdc.gov/Features/PoisonPrevention/.

3. Donn, J, Mendoza, M. and Pritchard, J. "Pharmaceuticals found lurking in U.S. drinking water." Associated Press. March, 2008. Available at <http://www.msnbc.msn.com/id/23503485/>, last visited January 2, 2009.

4. Phillips, P.J., Smith, S.G., Kolpin, D.W., Zaugg, S.D., Buxton, H.T., and Furlong, E.T., 2010, Method Description, Quality Assurance, Environmental Data, and other Information for Analysis of Pharmaceuticals in Wastewater-Treatment-Plant Effluents, Streamwater, and Reservoirs, 2004-2009: U.S. Geological Survey Open-File Report 2010-1102, 36 p., available at http://pubs.usgs.gov/of/2010/1102/.

5. Blazer VS. Indicators of Reproductive Endocrine Disruption in Fish in the Chesapeake Bay Watershed. United States: U.S. Geological Survey; 2012. Available from: http://www.chesapeakebay.net/channel_files/18061/intersexfish_final_usgs_draft march_23.pdf.

6. Atiken M. Avoidable Costs in U.S. Healthcare: The $200 Billion Opportunity from Using Medicines More Responsibly. United States: IMS Institute for Healthcare Informatics; 2013:1-56. Available from: www.theimsinstitute.org.

7. Hauser JM, Chen L, Paice J. Down the drain: the cost of medications wasted in hospice. J Pain Symptom Manage. 2006;31:379-380.

8. Tucker C. Drug takebacks aim to prevent abuse, protect environment: Disposing of medications the right way. The Nation's Health. 2011;41:1-15.

9. waste. Oxford Dictionaries. Oxford University Press. http://www.oxforddictionaries.com/us/definition/american_english/waste (accessed March 10, 2015).

10. White KG. UK interventions to control medicines wastage: a critical review. Int J Pharm Pract. 2010;18:131-140.

11. Abou-Auda HS. An economic assessment of the extent of medication use and wastage among families in Saudi Arabia and Arabian Gulf countries. Clinical therapeutics ,2003,Vol.25(4),p.1276-1292

12. Trueman P, Taylor D, Lowson K, et al. Evaluation of the scale, causes and costs of waste medicines. Report of DH funded national project. . 2010.

13. Nava-Ocampo AA, Alarcon-Almanza JM, Moyao-Garcia D, Ramirez-Mora JC, Salmeron J. Undocumented drug utilization and drug waste increase costs of pediatric anesthesia care. Fundam Clin Pharmacol. 2004;18:107-112.

14. Pharmaceutical Waste: Waste Fact Sheet. United States: Riverside County, Waste Management Department; 2014:1-2. Available from: http://www.rivcowm.org/opencms/WasteGuide/FactSheets/Pharmaceutical.pdf

15. Shrank WH, Choudhry NK, Fischer MA, et al. The epidemiology of prescriptions abandoned at the pharmacy. Ann Intern Med. 2010;153:633-640.

16. Bergeron AR, Webb JR, Serper M, et al. Impact of electronic prescribing on medication use in ambulatory care. Am J Manag Care. 2013;19:1012-1017.

17. Streeter SB, Schwartzberg L, Husain N, Johnsrud M. Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. J Oncol Pract. 2011;7:46s-51s.

18. Gleason P, Starner C, Gunderson B, Schafer J, Sarran H. Association of Prescription Abandonment with Cost Share for High-Cost Specialty Pharmacy Medications. Journal of Managed Care Pharmacy (USA).2009;15:648-58.

19. Papke JA. Unclaimed prescriptions requisitioned through provider order entry. Journal of Managed Care Pharmacy (USA). 1999;5:498-502.

20. Jackson TH, Bentley JP, McCaffrey DJ,3rd, Pace P, Holmes E, West-Strum D. Store and prescription characteristics associated with primary medication nonadherence. J Manag Care Pharm. 2014;20:824-832.

21. Fischer MA, Stedman MR, Lii J, et al. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. J Gen Intern Med. 2010;25:284-290.

22. Raebel MA, Ellis JL, Carroll NM, et al. Characteristics of patients with primary non-adherence to medications for hypertension, diabetes, and lipid disorders. J Gen Intern Med. 2012;27:57-64.

23. Kennedy J, Tuleu I, Mackay K. Unfilled prescriptions of Medicare beneficiaries: prevalence, reasons, and types of medicines prescribed. J Manag Care Pharm. 2008;14:553-560.

24. Ding R, Zeger SL, Steinwachs DM, Ortmann MJ, McCarthy ML. The validity of self-reported primary adherence among Medicaid patients discharged from the emergency department with a prescription medication. Ann Emerg Med. 2013;62:225-234.

25. Wroth TH, Pathman DE. Primary medication adherence in a rural population: the role of the patient-physician relationship and satisfaction with care. J Am Board Fam Med. 2006;19:478-486.

26. Achusim LE, Caselnova DA, Cosgrove R. Consequences of unclaimed prescriptions in a university health system. ASHP Midyear Clinical Meeting. 1998;33:P-374D.

27. Agi RO, Egbunike IG, Osemene NI, Plattenburg JP, Plattenburg P, Jackson DM. Evaluation and impact of unclaimed prescriptions in a county hospital district institution. ASHP Midyear Clinical Meeting. 1996;31:P-447E.

28. Berger Z, Kimbrough W, Gillespie C, et al. Lower copay and oral administration: predictors of first-fill adherence to new asthma prescriptions. Am Health Drug Benefits. 2009;2:174-180.

29. Bestvina CM, Zullig LL, Rushing C, et al. Patient-oncologist cost communication, financial distress, and medication adherence. J Oncol Pract. 2014;10:162-167.

30. Bonuck KA, Memmott MM, Arno PS. Cost related prescription drug misuse among older persons. J Res Pharm Econ. 2001;11:39-49.

31. Butler J, Arbogast PG, BeLue R, et al. Outpatient adherence to beta-blocker therapy after acute myocardial infarction. J Am Coll Cardiol. 2002;40:1589-1595.

32. Butler J, Arbogast PG, Daugherty J, Jain MK, Ray WA, Griffin MR. Outpatient utilization of angiotensin-converting enzyme inhibitors among heart failure patients after hospital discharge. J Am Coll Cardiol. 2004;43:2036-2043.

33. Campbell RK, Dixon LR. How to calculate the cost of filling a prescription. Pharmacy Times (USA). 1979;45:61-64.

34. Carroll NM, Ellis JL, Luckett CF, Raebel MA. Improving the validity of determining medication adherence from electronic health record medications orders. J Am Med Inform Assoc. 2011;18:717-720.

35. Cassidy KS, Szymaniak G, Whalen KM. Unclaimed prescriptions: outcomes of pharmacist interventions. ASHP Midyear Clinical Meeting. 1990;25:HMO--08.

36. Chan J, Choy GS, Ferrell B. Reasons and consequences of unclaimed prescriptions. ASHP Midyear Clinical Meeting. 1995;30:P-86(D).

37. Cline JC, Foster AC, Lee TJ, Pait LD. Unclaimed prescriptions in an outpatient pharmacy within an academic medical center. ASHP Midyear Clinical Meeting. 1998;33:P-376E.

38. Cobaugh DJ, Angner E, Kiefe CI, et al. Effect of racial differences on ability to afford prescription medications. Am J Health Syst Pharm. 2008;65:2137-2143.

39. Cohen Solal A, Leurs I, Assyag P, et al. Optimization of heart Failure medical treatment after hospital discharge according to left ventricular Ejection fraction: the FUTURE survey. Arch Cardiovasc Dis. 2012;105:355-365.

40. Cooke CE, Xing S, Lee HY, Belletti DA. You wrote the prescription, but will it get filled? J Fam Pract. 2011;60:321-327.

41. Craghead RM, Wartski DM. An evaluative study of unclaimed prescriptions. Hosp Pharm. 1991;26:616-7, 632.

42. Craghead RM, Wartski DM. Effect of automated prescription transmittal on number of unclaimed prescriptions. Am J Hosp Pharm. 1989;46:310-312.

43. Dong BJ, McCart GM, Lynch SS. Reducing unclaimed prescriptions through pharmacist intervention. Hospital Pharmacy (USA). 1998;33:841-846.

44. Dwinell AM, Tyler LS, Herr RD. Prescription filling after discharge from the emergency department. ASHP Midyear Clinical Meeting. 1992;27:P-443E.

45. Esposito D, Schone E, Williams T, et al. Prevalence of unclaimed prescriptions at military pharmacies. J Manag Care Pharm. 2008;14:541-552.

46. Eugenio KR, Griffin CR. Evaluation and characterization of unclaimed prescriptions at a university hospital ambulatory care pharmacy. ASHP Midyear Clinical Meeting. 1998;33:P-375E.

47. Farmer KC, Gumbhir AK. Unclaimed prescriptions: an overlooked opportunity. Am Pharm. 1992;NS32:55-59.

48. Galliher JM, Post DM, Weiss BD, et al. Patients' question-asking behavior during primary care visits: a report from the AAFP National Research Network. Ann Fam Med. 2010;8:151-159.

49. Hakim A. E-prescribing and primary noncompliance: physician and patient experience. Prof Case Manag. 2010;15:62-7; quiz 68-9.

50. Hamilton WR, Hetler TA, Hopkins UK. Study on the characteristics of prescription transmittal processes and the effect of a patient prescription reminder system on patient compliance. Journal of Managed Care Pharmacy (USA). 1998;4:174-178.

51. Hamilton WR, Hopkins UK. Survey on unclaimed prescriptions in a community pharmacy. J Am Pharm Assoc (Wash). 1997;NS37:341-345.

52. Harrison TN, Derose SF, Cheetham TC, et al. Primary nonadherence to statin therapy: patients' perceptions. Am J Manag Care. 2013;19:e133-9.

53. Holley JL, DeVore CC. Why all prescribed medications are not taken: results from a survey of chronic dialysis patients. Adv Perit Dial. 2006;22:162-166.

54. Huang JV, Casebeer AW, Plomondon ME, et al. Prescription-filling rates for key medications in Veterans Affairs patients after coronary artery bypass grafting. Am J Health Syst Pharm. 2004;61:1248-1252.

55. James TW, MacKeigan LD, Schneider PJ. Compliance-based evaluation of an emergency department starter pack system. ASHP Annual Meeting. 1992;49:P-117R.

56. Joslin J, Wojcik SM, Fisher A, Grant WD. Do free or low-cost antibiotic promotions alter prescription filling habits? Pharm Pract (Granada). 2014;12:416.

57. Ketcham JD, Simon KI. Medicare Part D's effects on elderly patients' drug costs and utilization. Am J Manag Care. 2008;14:SP14-22.

58. Kirking MH, Kirking DM. Evaluation of unclaimed prescriptions in an ambulatory care pharmacy. Hosp Pharm. 1993;28:90-1, 94, 102.

59. Kirking MH, Zaleon CR, Kirking DM. Unclaimed prescriptions at a university hospital's ambulatory care pharmacy. Am J Health Syst Pharm. 1995;52:490-495.

60. Kripalani S, Henderson LE, Jacobson TA, Vaccarino V. Medication use among inner-city patients after hospital discharge: patient-reported barriers and solutions. Mayo Clin Proc. 2008;83:529-535.

61. Lagu T, Weiner MG, Eachus S, Tang SS, Schwartz JS, Turner BJ. Effect of patient comorbidities on filling of antihypertensive prescriptions. Am J Manag Care. 2009;15:24-30.

62. Lash S, Harding J. Abandoned prescriptions: quantitative assessment of their cause. Journal of Managed Care Pharmacy (USA). 1995;1:193-199.

63. Liberman JN, Hutchins DS, Popiel RG, Patel MH, Jan SA, Berger JE. Determinants of primary nonadherence in asthma-controller and dyslipidemia pharmacotherapy. AM J PHARM BENEFITS. 2010;2:111-118.

64. Liberto RB, Davidson HE, Han LF. Compliance with cardiac medication therapy following discharge education and telephonic follow up in cardiac patients. ASHP Midyear Clinical Meeting. 2000;35:P-31R.

65. Lin A, Huang S, Chen Y. Analysis of prescriptions filling labor in community pharmacy. ASHP Summer Meeting. 2009;65.

66. Luckman R, Weisbuch JB, Taubman AH, King J, Little F, \ET/. Drug compliance\M/study of patient behavior based on medical records. Drug Intell Clin Pharm. 1979;13:136-143.

67. Lynch SS, Dong BJ, Louie T. Effect of pharmacist intervention in reducing the number of unclaimed prescriptions: descriptive report. ASHP Annual Meeting. 1993;50:P-74D.

68. McCaffrey DJ, Smith MC, Banahan BF. Why prescriptions go unclaimed. US Pharmacist (USA). 1993;18:58-65.

69. McCaffrey DJ, Smith MC, Banahan BF, Frate DA, Gilbert FW. Continued look into the financial implications of initial noncompliance in community pharmacies: unclaimed prescription audit pilot. Journal of Research in Pharmaceutical Economics (USA). 1998;9:33-57.

70. McCaffrey DJ, Smith MC, Banahan BF, Frate DA, Gilbert FW. Unclaimed prescription phenomenon: challenge for the community pharmacist. APhA Annual Meeting. 1996;143:71.

71. McCaffrey DJ, Smith MC, Banahan BF, Juergens JP, Szeinbach SL. Financial implications of initial noncompliance: investigation of unclaimed prescriptions in community pharmacies. Journal of Research in Pharmaceutical Economics (USA). 1995;6:39-64.

72. McCarthy ML, Ding R, Roderer NK, et al. Does providing prescription information or services improve medication adherence among patients discharged from the

emergency department? A randomized controlled trial. Ann Emerg Med. 2013;62:212-23.e1.

73. Montgomery CM, Blouch DL, Moussavian PA. Unclaimed antibiotic prescriptions in an outpatient pharmacy. ASHP Midyear Clinical Meeting. 1996;31:P-31R.

74. Oliveria SA, Menditto LA, Ulcickas Yood M, Koo YH, Wells KE, McCarthy BD. Barriers to the initiation of, and persistence with, insulin therapy. Curr Med Res Opin. 2007;23:3105-3112.

75. Peterson A. Adherence: Identifying the problem and selected interventions. ASHP Midyear Clinical Meeting. 2003;38:PI-104.

76. Reynolds K, Muntner P, Cheetham TC, et al. Primary non-adherence to bisphosphonates in an integrated healthcare setting. Osteoporos Int. 2013;24:2509-2517.

77. Saks EK, Wiebe DJ, Cory LA, Sammel MD, Arya LA. Beliefs about medications as a predictor of treatment adherence in women with urinary incontinence. J Womens Health (Larchmt). 2012;21:440-446.

78. Scholtz D, Ballentine R. Effect of pharmacist intervention on initial drug noncompliance and emergency room visits in asthmatic patients. ASHP Midyear Clinical Meeting. 1990;25:P-417E.

79. Serna MC, Cruz I, Real J, Gasco E, Galvan L. Duration and adherence of antidepressant treatment (2003 to 2007) based on prescription database. Eur Psychiatry. 2010;25:206-213.

80. Shah NR, Hirsch AG, Zacker C, Taylor S, Wood GC, Stewart WF. Factors associated with first-fill adherence rates for diabetic medications: a cohort study. J Gen Intern Med. 2009;24:233-237.

81. Solberg LI, Parker ED, Foldes SS, Walker PF. Disparities in tobacco cessation medication orders and fills among special populations. Nicotine Tob Res. 2010;12:144-151.

82. Suffoletto B, Calabria J, Ross A, Callaway C, Yealy DM. A mobile phone text message program to measure oral antibiotic use and provide feedback on adherence to patients discharged from the emergency department. Acad Emerg Med. 2012;19:949-958.

83. Taira DA, Iwane KA, Chung RS. Prescription drugs: elderly enrollee reports of financial access, receipt of free samples, and discussion of generic equivalents related to type of coverage. Am J Manag Care. 2003;9:305-312.

84. Tavitian SM. Impact of pharmacist intervention on unclaimed prescriptions. ASHP Midyear Clinical Meeting. 1996;31:P-69D.

85. Tavitian SM, Kidder PA, Shane R. Contacting patients with unclaimed prescriptions: pharmacist's impact on drug therapy concordance. Hosp Pharm. 2001;36:1060-1065.

86. Thomas EJ, Burstin HR, O'Neil AC, Orav EJ, Brennan TA. Patient noncompliance with medical advice after the emergency department visit. Ann Emerg Med. 1996;27:49-55.

87. Wilhardt MS, Sauer KA, McAllister DK. Barriers to filling emergency department discharge prescriptions. ASHP Midyear Clinical Meeting. 1998;33:P-138D.

88. Yu AP, Yu YF, Nichol MB, Gwadry-Sridhar F. Delay in filling the initial prescription for a statin: a potential early indicator of medication nonpersistence. Clin Ther. 2008;30:761-74; discussion 716.

89. Zaleon CR, Kirking MH, Kirking DM. Unclaimed prescriptions in a university hospital ambulatory care pharmacy: pharmacy and patient perspectives. ASHP Annual Meeting. 1993;50:P-73E.

90. Shin J, McCombs JS, Sanchez RJ, Udall M, Deminski MC, Cheetham TC. Primary nonadherence to medications in an integrated healthcare setting. Am J Manag Care. 2012;18:426-434.

91. Fischer MA, Choudhry NK, Brill G, et al. Trouble getting started: predictors of primary medication nonadherence. Am J Med. 2011;124:1081.e9-1081.22.

92. Wieczorkiewicz SM, Kassamali Z, Danziger LH. Behind closed doors: medication storage and disposal in the home. Ann Pharmacother. 2013;47:482-489

93. Lewis ET, Cucciare MA, Trafton JA. What do patients do with unused opioid medications? Clin J Pain. 2014;30:654-662.

94. Bates C, Laciak R, Southwick A, Bishoff J. Overprescription of postoperative narcotics: a look at postoperative pain medication delivery, consumption and disposal in urological practice. J Urol. 2011;185:551-555.

95. Morgan TM. The economic impact of wasted prescription medication in an outpatient population of older adults. J Fam Pract. 2001;50:779-781.

96. Cooke C. Take as directed: a prescription not followed New Survey Shows Improper Medication Use Reaching Crisis Proportions USA: The National

Community Pharmacists Association (NCPA); 2006. Available from: http://www.ncpanet.org/pdf/adherence/patientadherence-pr1206.pdf.

97. Gray-Winnett MD, Davis CS, Yokley SG, Franks AS. From dispensing to disposal: the role of student pharmacists in medication disposal and the implementation of a take-back program. J Am Pharm Assoc (2003). 2010;50:613-618.

98. Lystlund S, Stevens E, Planas LG, Marcy TR. Patient participation in a clinic-based community pharmacy medication take-back program. J Am Pharm Assoc (2003). 2014;54:280-284.

99. Pervanas H, Cooper M, Lenza R. Description of a Medication Disposal Event in a Managed Care Setting. Journal of Pharmacy Technology (USA). ;26:264.

100. Wooding F, Baroletti S, Collins A. Descriptive evaluation of a regional medication take-back event at a community hospital. ASHP Midyear Clinical Meeting. ;2011:P-383(D).

101. Perry LA, Shinn BW, Stanovich J. Quantification of an ongoing community-based medication take-back program. J Am Pharm Assoc (2003). 2014;54:275-279.

102. Garey KW, Johle ML, Behrman K, Neuhauser MM. Economic consequences of unused medications in Houston, Texas. Ann Pharmacother. 2004;38:1165-1168.

103. Law AV, Sakharkar P, Zargarzadeh A, et al. Taking stock of medication wastage: Unused medications in US households. Res Social Adm Pharm. 2014.

104. National Ambulatory Medical Care Survey: 2010 Summary Tables United States: CDC/NCHS, National Ambulatory Medical Care Survey; 2015:1-2. Available from: http://www.cdc.gov/nchs/data/ahcd/namcs_summary/2010_namcs_web_tables.pdf.

105. National Hospital Ambulatory Medical Care Survey: 2011 Outpatient Department Summary Tables United States: CDC/NCHS, National Hospital Ambulatory Medical Care Survey; 2015:1-2. Available from: http://www.cdc.gov/nchs/data/ahcd/nhamcs_outpatient/2011_opd_web_tables.pdf.

106. National Hospital Ambulatory Medical Care Survey: 2011 Emergency Department Summary Tables United States: CDC/NCHS, National Hospital Ambulatory Medical Care Survey; 2014:1-2. Available from: www.cdc.gov/nchs/data/ahcd/nhamcsemergency/2011edwebtables.pdf.

107. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23:1296-1310.

108. American Medical Association. cpt® Code/Relative Value Search. Available at: https://ocm.amaassn.org/OCM/CPTRelativeValueSearch.do?submitbutton=accept2014.

109. National Cost of Dispensing (COD) Study: Final Report. U.S.: Grant Thornton LLP; 2007:2-62.

110. Carroll N. Pricing pharmaceutical products and services. In: Troy D, Brittain M, Meyer B, eds. Financial Management for Pharmacists A Decision-Making Approach. Third Edition ed. ; 2007:127-130

111. Shaw J, Zachry W. Application of probabilistic sensitivity analysis in decision analytic modeling. Formulary (USA). 2002;37:32-40.

112. Holdford DA, Inocencio TJ. Adherence and persistence associated with an appointment-based medication synchronization program. J Am Pharm Assoc (2003). 2013;53:576-583.