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Automated Analysis of Polypharmacy using Prescription Drug Claims Data

Shahad Nagoor

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Automated Analysis of Polypharmacy using Prescription Drug Claims Data

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Thesis submitted to the
Benjamin M. Statler College of Engineering and Mineral Resources
at West Virginia University

in partial fulfillment of the requirements
for the degree of

Master of Science

in

Computer Science

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Abstract

Automated Analysis of Polypharmacy using Prescription Drugs Claims Data

Shahad Nagoor

Patients are often prescribed with multiple medications, especially those with chronic conditions. This leads to the possibility of concurrent use of multiple medications in overlapping time intervals. Clinical studies have shown that polypharmacy has a substantial impact on health outcomes. Increasing the number of medications that an individual or a patient takes increases the likelihood that the individual or patient would have an adverse drug event, drug misuse, drug overdose, or reduced therapeutic effect of the drugs. These problems are often behind emergency room admissions in hospitals. Thus, studying polypharmacy problems and ways to resolve them have long been of great interest to health care professionals.

In this thesis, we focus on analyzing polypharmacy based on information extracted from prescription drug claims data. Prior work has defined polypharmacy, based mainly on the number of drugs, or the number of drug classes. Here, we emphasize the use of drug active ingredients as another basis for definition of polypharmacy. Then, we develop an algorithm for automated determination of the thresholds required for each of the different definitions of polypharmacy. Based on this, we perform a comparative analysis of the different approaches to polypharmacy. We analyzed the possible association between levels of polypharmacy and ER visits. Independent of the basis used for the polypharmacy definition, the results showed a general increase in ER problems with increasing number of drugs/drug classes/or active ingredients. However, the threshold for polypharmacy varied with the specific basis used in the definition. This observation led to a composite definition of polypharmacy, involving the use of a combination of different basic elements at the same time, rather than the current practice of using one single element. Further computational analysis included studying the occurrence of single-elements (e.g., single drugs, single classes, or single active ingredients), and the co-occurrence of multiple elements of the same basic type (e.g., two-drugs, two drug classes, two active ingredients, three-drugs, three drug classes, three active ingredients, etc.). This provides a repository of incidences of common drugs, active ingredients, drug class polypharmacy combinations, along with their richness, which can be a basis for further studies in drug safety and drug efficacy.

The results from this work provides a framework for healthcare specialists to analyze the impact of each polypharmacy definition and their respective associations with emergency room (ER) visits, and which combinations of drugs, of drug classes, or of active ingredients are likely to result in significant hospitalization, and thus should be avoided.

Dedication

To my husband 'Foad', my son 'Mohammed', my daughter 'Danah' and our parents, sisters and brothers.

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TABLE OF CONTENTS

TABLE OF CONTENTS	v
LIST OF ABBREVIATIONS.....	vii
LIST OF FIGURES	viii
LIST OF TABLES	x
CHAPTER 1 INTRODUCTION	1
1.1 PROBLEM AND MOTIVATION	1
1.2 THESIS CONTRIBUTIONS	2
1.3 THESIS OUTLINE	2
CHAPTER 2 BACKGROUND AND RELATED WORK	3
2.1 PROBLEM OF POLYPHARMACY.....	3
2.2 DEFINITIONS OF POLYPHARMACY.....	4
2.3 POLYPHARMACY -- THE GOOD AND THE BAD.....	4
2.4 METHODS OF DETECTION AND TYPES OF DATA USED.....	5
CHAPTER 3 METHODOLOGY	7
3.1 THREE DEFINITIONS OF POLYPHARMACY.....	7
3.1.1 Defining polypharmacy using number of drugs.....	7
3.1.2 Defining polypharmacy using number of drug classes.....	7
3.1.3 Defining polypharmacy using active ingredients	9
3.2 DETECTING POLYPHARMACY	11
3.3 AUTOMATED THRESHOLD FOR POLYPHARMACY.....	14
3.4 REDEFINING POLYPHARMACY.....	15
3.5 COMPUTATIONAL ANALYSIS FOR THE THREE DEFINITIONS.....	16
3.5.1 Prevalence.....	16
3.5.2 Association of polypharmacy with ER.....	17
3.5.3 Richness and over-representations.....	18
CHAPTER 4 RESULTS.....	20
4.1 DATASET	20
4.2 PREVELANCE	21

4.2.1	Prevalence of polypharmacy using number of drugs	21
4.2.2	Prevalence of polypharmacy using number of Active ingredients	25
4.2.3	Prevalence using number of drug classes	32
4.2.4	Prevalence summary.....	41
4.3	ASSOCIATION OF POLYPHARMACY WITH ER	42
4.3.1	Relating drugs polypharmacy to ER	42
4.3.2	Relating active ingredients polypharmacy to ER	45
4.3.3	Relating classes polypharmacy to ER	48
4.4	RICHNESS AND OVER-REPRESENTATION	55
4.4.1	Richness of drug polypharmacy	55
4.4.2	Richness of active ingredients polypharmacy	60
4.4.3	Richness of drug classes polypharmacy.....	66
4.5	AUTOMATED THRESHOLDS FOR POLYPHARMACY.....	85
4.5.1	Delta Function.....	85
4.5.2	Choosing Polypharmacy Thresholds	91
4.5.3	Redefining polypharmacy.....	92
CHAPTER 5	CONCLUSION	95
5.1	LIMITATIONS	96
5.2	FUTURE WORK.....	96
REFERENCES.....		97
APPENDICES.....		100
A	TC1S1 Class Codes and Names.....	100
B	Associations of three-element polypharmacy with ER.....	104
C	Richness of three-element polypharmacy.....	121

LIST OF ABBREVIATIONS

PP	Polypharmacy
ER	Emergency Room
AI	Active ingredients
TC1	MULTUM THERAPEUTIC CLASS #1
TC1S1	MULTUM THERAPEUTIC SUB-CLASS #1 FOR TC1

LIST OF FIGURES

Figure 3.1 General work flow of our methodology	12
Figure 3.2 Polypharmacy detection algorithm	13
Figure 4.1 Ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of drugs.....	44
Figure 4.2 Proportion of ER visits for given polypharmacy groups based on the number of drugs.....	44
Figure 4.3 The probability that a patient in a given polypharmacy group will visit ER in a given year.....	45
Figure 4.4 Ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of active ingredients.....	47
Figure 4.5 Proportion of ER visits for given polypharmacy groups based on the number of active ingredients.....	47
Figure 4.6 The probability that a patient in a given polypharmacy group will visit ER in a given year.	48
Figure 4.7 Ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of TC1 drug class.....	50
Figure 4.8 Proportion of ER visits for given polypharmacy groups based on the number of TC1 drug class.....	50
Figure 4.9 The probability that a patient in a given polypharmacy group will visit ER in a given year.....	51
Figure 4.10 Ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of TC1S1 drug class.....	53
Figure 4.11 Proportion of ER visits for given polypharmacy groups based on the number of TC1S1 drug class.....	53
Figure 4.12 The probability that a patient in a given polypharmacy group will visit ER in a given year.....	54

Figure 4.13. drug pair occurrence richness plotted against drug pair ER occurrence richness in log scale.....	59
Figure 4.14. Relationship between active ingredients occurrence and ER richness using a log scale (logarithms are in base 10).....	66
Figure 4.15. relationship between TC1 class pairs occurrence and ER richness. Logarithms are in base 10.	71
Figure 4.16. Relationship between TC1S1 class pairs occurrence and ER richness. Logarithms are in base 10.	77
Figure 4.17. Values of $\Delta(K,1)$ for drug PP vs. ER measure for years (2011- 2015).....	86
Figure 4.18. Values of $\Delta(K,1)$ for active ingredients PP vs. ER measure of years (2011- 2015)	87
Figure 4.19. Values of $\Delta(K,1)$ for TC1 class PP vs. ER measure of years (2011-2015).....	88
Figure 4.20. Values of $\Delta(K,1)$ for TC1S1 class PP vs. ER measure for years (2011- 2015).....	89
Figure 4.21. Values of $\Delta(K,1)$ for all PP vs. ER measure of years (2011-2015).....	90
Figure 4.22. compares #ER/#PP for all possible definitions of polypharmacy.....	93

LIST OF TABLES

Table 3.1: The 19 drug classes in TC1 used in this work	8
Table 4.1: Summary of MEPS dataset characteristics.....	20
Table 4.2: Statistics on prevalence of polypharmacy based on number of drugs.....	21
Table 4.3: Top 30 single-drugs in the dataset ranked by their occurrences.....	22
Table 4.4: Top 30 two-drug polypharmacy ranked by their occurrences.....	23
Table 4.5: Top 30 three-drug polypharmacy ranked by their occurrences.....	24
Table 4.6: Statistics on Prevalence of Polypharmacy using number of active ingredients.....	25
Table 4.7: Top 30 single-ingredients polypharmacy ranked by their occurrences.....	26
Table 4.8: Top 30 two-active ingredient polypharmacy ranked by their occurrences.....	27
Table 4.9: Top 30 three-active ingredient polypharmacy ranked by their occurrences..	28
Table 4.10: List of ingredients/substances matched with their parent drugs.....	29
Table 4.11: Prevalence of polypharmacy using number of drug classes	32
Table 4.12: Single TC1-class polypharmacy ranked by their occurrences	33
Table 4.13: Top 30 two TC1-class polypharmacy ranked by their occurrences.....	34
Table 4.14: Top 30 three TC1-class polypharmacy ranked by their occurrences.....	35
Table 4.15: Top 30 single TC1S1-classes in the dataset ranked by their occurrences.....	37
Table 4.16: Top 30 two-TC1S1 classes polypharmacy ranked by their occurrences.....	38
Table 4.17: Top 30 three-TC1S1 classes polypharmacy ranked by their occurrences.....	39
Table 4.18: Summary of prevalence 2011 -2015.....	41
Table 4.19: Proportion of single-element, two-element, and three-element of polypharmacy of all definitions.....	41

Table 4.20: Three measures relating the number of drugs in polypharmacy groups to ER visits.....	43
Table 4.21: Three measures relating the number of active ingredients in polypharmacy to ER visits	46
Table 4.22: Three measures relating the number of TC1 classes in polypharmacy to ER visits	49
Table 4.23: Three measures relating the number of TC1S1 classes in polypharmacy to ER visits	52
Table 4.24: Summary of average values for all definitions and for all years.....	54
Table 4.25: Top 30 drug-pairs and their co-occurrences probability ranked by ER total.....	56
Table 4.26: Individual and joint probability of occurrence for the top 30 two-drug polypharmacy (sorted by ER total) with richness of occurrence and ER.....	57
Table 4.27: Examples of drug pairs with high occurrence richness and low ER richness, high occurrence richness and low ER richness, and low occurrence richness and high ER richness.....	59
Table 4.28: Top 30 active ingredient-pairs and their co-occurrences probability ranked by ER total.....	61
Table 4.29: Individual and joint probability of occurrence for the top 30 two-active ingredient polypharmacy (sorted by ER total) with richness of occurrence and ER.....	62
Table 4.30: Comparison of some single drugs and their continent active ingredients ranking based on ER visits along with the richness of the active ingredient pairs.....	63
Table 4.31: Examples of active ingredient pairs with high occurrence richness and low ER richness, high occurrence richness and low ER richness, and low occurrence richness and high ER richness.....	64
Table 4.32: Top 30 TC1 class-pairs and their co-occurrences probability ranked by ER total.....	66

Table 4.33: Individual and joint probability of occurrence for the top 30 two-TC1 class polypharmacy (sorted by ER total) with richness of occurrence and ER.....	68
Table 4.34: Example of TC1 class pairs with high occurrence richness and low ER richness, high occurrence richness and low ER richness, and low occurrence richness and high ER richness.....	71
Table 4.35: Summary of Top 30 TC1 class pairs and their richness with respect to occurrence and ER.....	72
Table 4.36: Top 30 TC1S1 class-pairs and their co-occurrences probability ranked by ER total.....	74
Table 4.37: Individual and joint probability of occurrence for the top 30 two-TC1S1 class polypharmacy (sorted by ER total) with richness of occurrence and ER.....	75
Table 4.38: Examples of TC1S1 class pairs with high occurrence richness and low ER richness, high occurrence richness and low ER richness, and low occurrence richness and high ER richness.....	78
Table 4.39: Comparison of some single TC1 classes and some of their continent TC1S1 class pairs ranking based on ER visits along with the richness of the TC1S1 class pairs.....	80
Table 4.40: Two TC1 classes and their TC1S1 subclasses.....	80
Table 4.41: Comparison of some TC1 class pairs and some of their continent TC1S1 class pairs ranking based on ER visits along with their richness values.....	82
Table 4.42: Summary of ER richness occurrence for the top 20 polypharmacy using each definition ranked by #ER visits.	83
Table 4.43: Values of $\Delta(K,1)$ for drugs PP vs. ER measure for years (2011-2015).....	86
Table 4.44: Values of $\Delta(K,1)$ for active ingredient PP vs. ER measure for years (2011-2015).....	87
Table 4.45: Values of $\Delta(K,1)$ for TC1 class PP vs. ER measure of years (2011- 2015)....	88
Table 4.46: Values of $\Delta(K,1)$ for TC1S1 class PP vs. ER measure of years (2011- 2015).....	89

Table 4.47: Average values of $\Delta(K,1)$ for all PP vs. ER measure of years (2011-2015)...	90
Table 4.48: Summary statistics on the values for the delta function ($\Delta(K,1)$), and the minimum k value at which $\Delta(K,1) \geq 0.50$	91
Table 4.49: Measuring #ER/#PP for all possible definitions of polypharmacy.....	92

Chapter 1: Introduction

1.1 Problem and Motivation

From daily supplements to life-saving medications, patients are likely to be using multiple medications including prescription drugs and over the counter medications. This is especially the case for those patients that suffer from chronic conditions. This could lead to the concomitant use of multiple medications in overlapping time intervals. Taking multiple medications at the same time has been described as polypharmacy.

Polypharmacy has no standard definition. It basically has been defined as using more than one medication but with no specific upper boundary. An example definition is the standard deviation above the mean number of medications [1]. Others used 2, 3, 5, 10 or more medications [2]. A study of polypharmacy in the U.S. showed that 10% of the population and 30% of older adults in the US take five or more drugs at the same time [3]. This is because each chronic disease often results in prescription of multiple medications based on current medical practice guidelines. “An elderly patient with at least two disease states, such as heart failure and chronic obstructive pulmonary disease, will usually exceed this arbitrary threshold of > five medications” [2]. These guidelines have no strict monitoring requirement and thus patients could be subjected to over-prescription [3].

Studies have shown that polypharmacy has significant implications on peoples’ health [4,5]. The term “Polypharmacy” is not necessarily negative per se. However, polypharmacy raises the likelihood for someone, especially those who take large number of medications, to have an unhealthy mixture of medications. In other words, polypharmacy increases the risk of adverse drug events, drug-interactions, medication non-adherence, decreased functional status and geriatric syndromes or, misuse, overuse, and underuse of those medications [6]. Thus, for some people, the term polypharmacy evokes more of the negative consequences. The more the number of drugs, the higher the risk of these problems [7].

In their book, Neel and Hogan [8] reported that based on studies, polypharmacy would be classified as the fifth leading cause of death in the United States. It is also shown that polypharmacy was behind 28% of all hospital admissions [8]. Morbidity and mortality in health care are highly associated with adverse drug reactions (ADRs). ADRs are responsible for more than 3.5 million physician office visits and 1 million emergency department visits each year [9]. The Institute of Medicine reported up to 98,000 annual deaths resulting from medical errors in 2000. 7,000 deaths among them were caused by ADRs [2,10]. In 2016, the overdose deaths were up to 63,600 [10].

Many emergency room cases involve such drug events. Unfortunately, and above all, polypharmacy also leads to increased health care costs for both the patient and the general healthcare system [7,11]. Thus, research have used different methods and techniques that contribute to optimize people's health by reducing polypharmacy with potential risk.

Although identifying polypharmacy and its potential risks has long been of interest to health care professionals, it has also been challenging, given the complexity and diversity of patients' data. Medical datasets are often huge, disparate, and more importantly, confidential. In addition to this, the uncertainty about the correct way to define the term "polypharmacy" places another challenge for recognizing and analyzing polypharmacy problems. Therefore, such analysis need to be enhanced by the use of automated algorithms for adjustable identification of the incidence of polypharmacy as well as estimating the potential risks for the patients involved.

1.2 Thesis Contributions

The contributions of this thesis are summarized as follows:

- We propose a new definition of polypharmacy using drug active ingredients as the basic element.
- We propose a new method for determining thresholds of polypharmacy using the number of drugs, active ingredients and drug classes. Based on the new thresholds, we propose a refinement to the definition of polypharmacy and analyze the impact of this refinement.
- We provide a detailed computational analysis of polypharmacy, providing a basis for comparative analysis of different definitions of polypharmacy on a popular dataset.

1.3 Thesis Outline

Chapter 2 provides a background on the problem of polypharmacy and a literature survey of relevant studies on polypharmacy with a brief discussion of their limitations. Chapter 3 introduces three definitions of polypharmacy, our methodology for detecting polypharmacy sets, and automated approach to determining polypharmacy thresholds. Chapter 4 presents the dataset used in this study and the results of our detailed statistical analysis of polypharmacy. Finally, Chapter 5 provides our overall conclusions as well as future work and recommendations.

Chapter 2: Background and Related Work

2.1 Problem of polypharmacy

Studying polypharmacy problems have long been of great interest to health care professionals. Researchers have been looking for methods by which they can reliably evaluate the group of medications taken together to get answers about whether they are helpful, risky, or even unneeded. For this to be answered, an agreement on a standard way to define polypharmacy has to be reached in order to formalize what would be considered a polypharmacy and subsequently resolve its issues with higher consistency. Unfortunately, the definition of the term “polypharmacy” has been controversial topic in the health sciences literature.

According to the Viktil et al [12], the lack of a universal definition of polypharmacy makes it problematic to place effective measures to reduce it. This is because it depends on multiple factors such as the number of medications, the status of the patient’s health, and the actual combination of medications being taken in that polypharmacy. Such measures should assist in avoiding inappropriate polypharmacy, but at the same time should not eliminate the appropriate multi-drugs that are to improve quality of live for some patients with chronic conditions. In particular, reducing polypharmacy should not lead to undertreatments. As a consequence of this, the threshold by which polypharmacy should be defined has remained unspecified, making the definition imprecise, and the line between useful and harmful polypharmacy very blurry. Thus, studies of polypharmacy have used different definitions for the term “polypharmacy”. Some studies examine polypharmacy issues by considering the number of certain elements involved in the group of medications. In fact, the specific number that constitute the polypharmacy is in turn debatable.

The multiple faces for polypharmacy also involve considering the type of data or medical element used as basis for its definition. The literature involves some studies that used the actual number of drugs [1,2,4,7,17], and others that used the number of drug classes [18,19,20]. This makes a substantial difference for polypharmacy results. For instance, the polypharmacy of two or more drugs that are classified by the same drug class is not considered a polypharmacy by the definition of drug classes.

In addition to the problem of defining polypharmacy, predicting polypharmacy problems has been performed based on multiple variables. In particular, some studies use the number of drugs or drug classes as a leading predictor for problems. Others consider the actual combinations of drugs and drug classes. On the other hand, Jirón et al has shown that [Trends in prevalence and determinants of potentially inappropriate prescribing in the United States: 2007 to 2012]”The strongest predictor of PIM use was the number of drugs dispensed.”, and Scott et al [Reducing Inappropriate Polypharmacy The Process of Deprescribing] has concluded that “the

single most important predictor of inappropriate prescribing and risk of adverse drug events in older patients is the number of prescribed drugs". Yet, according to the study [16], "numbers in polypharmacy are not the enemy, it is rather the ineffective, harmful, unnecessary manner of prescribing". Also, Kantor et al [14] pointed out that documenting the actual patterns of prescriptions is essential for both the clinical practitioners and researchers.

This also poses a conflict for researchers who study polypharmacy problems and makes defining polypharmacy challenging, ambiguous, and above all, necessary.

2.2 Definitions of polypharmacy

Kantor et al [14] consider a polypharmacy as 5 or more prescription drugs. Jyrkkä et al [15] classified polypharmacy into three groups, namely: non-polypharmacy group (0-5 drugs) polypharmacy (6 to 9 drugs), and excessive polypharmacy group (10 or more drugs).

In [12], Viktil et al reported that some studies used different classifications: minor polypharmacy with 2-4 drugs and major polypharmacy with 5 or more drugs. Others used: 2 or more drugs, 3 or more, 5 or more, 6 or more, 10 or more, but the most common number used to define polypharmacy was 5. As reported in the literature, some studies used the actual drugs [1,2,4,7,17], while others used drug classes [18,19,20,21].

2.3 Polypharmacy -- The Good and The Bad

Polypharmacy could have positive or negative effects on patients. In [12] Viktil et al emphasized the janus face of polypharmacy and the importance of exploring the common recognition of the negative outcomes of polypharmacy. The janus face can be illustrated as avoiding the excessive use of drugs but also keeping the appropriate drugs that help reduce morbidity and are essential for improving the quality of life for people with multiple chronic conditions. Consequently, it is important to use the term polypharmacy with caution and not completely associate it with the negative consequences, as there could be necessary and useful polypharmacy.

Steinman [16] also pointed out the good aspect of some polypharmacy. According to his study, multidrug therapy can benefit older adults with multiple chronic diseases and are often considered necessary in managing such chronic conditions with their high level of comorbidity.

Jyrkkä et al [15] classified polypharmacy into three groups, namely: non-polypharmacy group (0-5 drugs) polypharmacy (6 to 9 drugs), and excessive polypharmacy group (10 or more drugs). In this study, interviews were done for elderly people of ages 75 and above in the first phase of analysis for data from 1998 to 2002. The second phase of analysis were conducted for survivors aged 80 and above in years 2003 to 2007. In their methodology, they performed advance regression to study the association that relates polypharmacy status and mortality.

Their findings pointed out that the excessive polypharmacy is considered to be a main indicator for mortality in old people.

The study by Qato et al [13] performed a descriptive analysis for elderly of ages (62 to 85) in a nationally representative sample in the U.S. Interviews were conducted in 2005-2006 and in 2010-2011 and polypharmacy were defined as taking at least 2 drugs at the regular use including prescriptions, over the counter, and dietary supplements. The extracted combinations were examined by Micromedex for drug-drug interaction examination. Their results showed an increase in the usage of interacting medications over time, and 15% of the subjects having the potential to be exposed to major interactions. Their analysis included prevalence of drugs and drug classes, and they estimated harmful interactions at the drug level.

Abe et al [24] conducted a study in Japan in which they attempted to connect polypharmacy results with emergency room visits. Statistical analysis on those visits showed that 69% of 3084 adult patients transported to hospital by ambulance, had polypharmacy. The mean number of their polypharmacy ranges from 3 to 6. About 7% of patients had drug adverse events.

2.4 Methods of detection and types of data used

Maher et al [2] discussed the negative consequences of polypharmacy in Ambulatory Care, Hospital Setting, Nursing Home Setting and proved by evidence studies that intervention by inter-professional were effective in reducing unnecessary medications. Similar study was done by Zarowitz et al in 2012 [25]. Their objectives were to reduce polypharmacy risks, and cost. The intervention program involves clinical pharmacists. They performed a review for drug therapy and then contacted with physicians and patients to enhance their awareness about polypharmacy problems and solutions.

Rambhade et al conducted a study in India [6] that used a Questionnaire-based approach to analyze polypharmacy and its consequences. Patients were interviewed at pharmacy shops and their prescriptions were copied for the analysis. They found that 2.38% of the prescriptions showed over prescribing. 3.96% showed repetition, while 2.39% showed drug-drug interactions. Then, they suggested a list of criteria that should be followed by prescribers for the sake of reducing inappropriate medications use.

In another study, Garfinkel et al [26], discussed and summarized the main international approaches to refine clinical and economic outcomes of inappropriate medication use and polypharmacy(IMUP) which involve clinical, pharmacological, computer-assisted and educational programs. By multiple studies reviews, it has been shown that using computer based prescription support system contributed in eliminating IMUP and severe drug–drug interactions.

Grando et al [27] used an ontology-based representation of drugs and their interactions after reviewing existed drugs knowledgebase and built a system for assigning complexity to drug prescription using multiple factors such as dosage and frequency. This complexity was used later by a decision support system to estimate safety of polypharmacy prescriptions.

Makar et al [28] used machine learning classifiers for prediction of six-month mortality in elderly people using Medicare claims data. They refined the features obtained from the best of traditional models and included not only the presence of diseases but also measures of their severity. This resulted in an augmented feature set that were tested using six classifiers. Their results outperformed traditional measures of mortality predictions that had been used in medical literature. This provides a prognostic tool that can be used in patient-physician decisions about end of life care and treatment options.

To sum up, prior work has studied multi-drug problems but never agreed on the exact definition of polypharmacy, the definite number for polypharmacy elements, the basic type of element used to define polypharmacy (i.e, drugs, drug-classes, etc). In this study, we investigate multiple definitions for polypharmacy derived from prior work in the literature and propose two more ways to define polypharmacy, the concomitant use of multiple medications. Next chapter introduces the definitions of polypharmacy and considers their advantages and limitations. This is followed by the methodology used in this work to analyze and compare the current and proposed definitions.

Chapter 3: Methodology

3.1 Three definitions of polypharmacy

We start our analysis by first considering the different definitions of polypharmacy. In particular, we consider three definitions that differ in the key data type used as the basis for the definitions.

3.1.1 Defining polypharmacy using number of drugs

Defining polypharmacy using the number of drugs has been considered the classic and the most popular method used for studying polypharmacy. For instance, studies in [1,2,4,7,17] used multi-drugs as their polypharmacy definition. Researchers have used this definition to look for harmful drug-drug interactions. This has been beneficial in recognizing risks at the drug level. However, the problems resulting from drugs could still be unspecified using this definition. In particular, this method may flag that using certain number or patterns of drugs as problematic but not provide sufficient justification on how could two or more drugs that are used together could interact negatively. In fact, this method also does not take into account potential problems with single drugs, as they are not considered as polypharmacy by the nature of this definition.

Thus, although this drug-based polypharmacy definition has provided useful recognition of some problems of using multiple-drug, there is still a need for a more detailed method by which the ambiguity or uncertainty behind single drug-related problems and even multiple-drug adverse reactions could be resolved and better explained. Investigating drug problem can be significantly enhanced by considering drug ingredients. Those ingredients may interact with each other, inhibit each other, enhance each other and therefore lead to misuse or overdose of certain substances. Although examining drugs ingredients should be intuitive, to our knowledge there is only one study prior to this work has considered the drug polypharmacy problem at the drug ingredients level. Section 3.1.3 will provide more detailed discussion about defining polypharmacy by drug ingredients.

3.1.2 Defining polypharmacy using number of drug classes

Medications are classified to groups using different criteria. They could be classified based on similarity of chemical structure, or the way they work, or the purpose for which they are used for.

For instance, Aspirin and sulfasalazine are classified as Salicylates based on similarity of their chemical structure. Aspirin is also classified as NSAID (Nonsteroidal anti-inflammatory drug). This class also contains Ibuprofen and Naproxen. Those medications are used for relieving mild to moderate pain such as mild joint inflammation and rheumatic fever. Also, Aspirin work on preventing blood clots, belonging to the class of medications called anti-platelets.

In general, patients should not be prescribed with two or more medications that share the same class since they may result in risks of overdose. Defining polypharmacy based on the

drug classes has been used in the literature for beneficial monitoring of patients' medications prescriptions and examining their safety at the drug-class level. See [18,19,20,21] for examples.

Researchers have used drug classes as the basic type to define polypharmacy because different classes may have different mechanisms of action. Based on this perspective, drugs that belong to the same class may not be considered as polypharmacy, but rather it would be considered as combinational therapy. Thus, this approach to define polypharmacy identifies the poly-mechanisms embedded in the prescribed drugs, which could not be captured by the definition of polypharmacy using the number of drugs.

A popular drug classification system is the Anatomical Therapeutic Chemical (ATC) classification systems. ATC classification system classifies drugs and their active ingredients based on the body organ or system that the drugs are expected to act on [22]. The therapeutic classes are defined according to the Multum/Lexicon therapeutic classification system [30]. In this work, we consider two therapeutic classes known as TC1 and TC1S1 for Therapeutic classes and Therapeutic sub-classes, respectively. TC1 assigns a drug to one or more therapeutic/chemical categories. Drugs can have up to three categories per drug while TC1S1 assigns one or more sub-categories to a more general therapeutic class category given to a drug.

An example of these therapeutic classes is cardiovascular agents which include calcium channel blockers and diuretics sub classes. Likewise, central nervous system agents is a superclass for analgesics, anticonvulsants, and antiparkinson agents. Gastrointestinal agents contain the three subclasses: H2-receptor antagonists, antacids, antidiarrheals, and proton pump inhibitors. Metabolic agents cover antihyperlipidemic agents and antidiabetic agents. Psychotherapeutic agents include the subclass of antidepressants and antipsychotics. More information about these classifications and other types of classifications can be found at the Medical Expenditure Panel Survey website [29]. Table 3.1 shows the 19 drug classes in TC1 used in this work. Table 1 in Appendix A shows the 133 drug-sub classes in TC1S1. The relationship between TC1 and TC1S1 classes can be found at Multum Lexicon documentation [31].

Table 3.1 The 19 drug classes in TC1 used in this work.

Class code	Class Name
-9	Not ascertained
1	Anti-infectives
19	Antihyperlipidemic agents
20	Antineoplastics
28	Biologicals
40	Cardiovascular agents
57	Central nervous system agents
81	Coagulation modifiers
87	Gastrointestinal agents
97	Hormones/hormone modifiers
105	Miscellaneous agents
113	Genitourinary tract agents
115	Nutritional products

122	Respiratory agents
133	Topical agents
218	Alternative medicines
242	Psychotherapeutic agents
254	Immunologic agents
331	Radiologic agents
358	Metabolic agents

Using drug classes for the purpose of recognizing polypharmacy issues can give a general idea about similar drug characteristics that are easier to remember for physicians and health care professionals. Yet it makes the association with health problems non-specific knowing that a class could include hundreds of drugs as members. Therefore, it could be misleading to rely on co-prescribed drug-classes alone, since classes are composed of drugs that also work on multiple targets [23]. As indicated earlier in this section, these classes have been used to define polypharmacy in prior work. However, the problems of polypharmacy using drug classes have not been very well studied as compared with the corresponding use of number of drugs in analyzing polypharmacy. Thus, in our study we map drugs to drug classes and generate lists of drug class combinations. We then checked these combinations for association with the number of emergency room visits and compared the results with those of drugs and drug-ingredients.

3.1.3 Defining polypharmacy using active ingredients

Medications consists of multiple substances. These substances are classified as active ingredients and inactive ingredients or excipients. Inactive ingredients are used to stabilize medications and generally have no pharmacological effect. In particular, they often involve preservatives, and flavoring agents. On the other hand, active ingredients are those that have biological or pharmacological activity for treating a condition. As an example, consider the medication Childrens Tylenol Plus Multi-Symptom Cold. This medication contains four active

ingredients, namely, ACETAMINOPHEN, CHLORPHENIRAMINE MALEATE, DEXTROMETHORPHAN HYDROBROMIDE, and PHENYLEPHRINE HYDROCHLORIDE.

An instance for a polypharmacy defined on the basis of drugs is (**ProCoMycin**, **Symbyax**, **Nighttime Multi-Symptom Cold**, **Marcaine**).

So, this polypharmacy includes four medications. On the other hand, the active ingredients polypharmacy resulting from these four medications contains 13 ingredients. They are listed below in the format: **medication** = [active ingredients A; active ingredients B,...etc.].

ProCoMycin = [BACITRACIN; NEOMYCIN; POLYMYXIN B; LIDOCAINE HYDROCHLORIDE]

Symbyax = [OLANZAPINE; FLUOXETINE HYDROCHLORIDE]

Nighttime Multi-Symptom Cold = [ACETAMINOPHEN; CHLORPHENIRAMINE MALEATE; DEXTROMETHORPHAN HYDROBROMIDE; PHENYLEPHRINE]

Marcaine = [BUPIVACAINE HYDROCHLORIDE ANHYDROUS; EPINEPHRINE BITARTRATE]

Based on the above, and as discussed earlier in Section 3.1.1, it can be seen that ingredients-based polypharmacy can produce a more detailed list of substances that a patient consumes and thus safety and efficacy of polypharmacy can be studied using data inputs at a finer level of granularity.

In particular, considering polypharmacy by active ingredients can expose potentially hidden patterns of risky (though unintentional) mix of substances resulting in possible unintentional overdose. Thus, defining polypharmacy using active ingredients can uncover the possibility for multiple substances taken, while embedded within one drug. The result is that even though one drug may not be considered as polypharmacy using the drug-based polypharmacy, it could be counted as polypharmacy when we use active ingredients as the basis of polypharmacy. However, it is also worthwhile to mention that getting the active ingredients of all existing drugs is challenging and not straightforward, given that there might be many ingredients with long and inconsistent names provided in the few datasets with this information, and these datasets are often incomplete.

To our knowledge, only one study [3] has used active ingredients in its definition of polypharmacy. Thus, our study is among the first studies that focus on establishing patterns of polypharmacy based on active ingredients and analyzing their impact on patients and their health outcomes. We use this definition of polypharmacy to compose a dataset of active ingredients combinations, and study their relationships with emergency room visits for the given patients. We compare the results of this definition of polypharmacy with the results of other methods discussed earlier. Comparing different definitions of polypharmacy can lead to answers to key questions about which method of defining polypharmacy could lead to improved discovery of associations between polypharmacy and general health problems, e.g., emergency room visits. This also enables us to consider the definitions as complementary sub-definitions for polypharmacy rather than using them separately and viewing them as alternative definitions.

We will build on this view of the different definitions as representing different levels of information about the medications being used by a given subject to propose a refinement of the definition of polypharmacy.

The next section introduces the methodology we use to detect polypharmacy. Detection algorithm is essentially independent of the specific element or level of information used in the definition of polypharmacy.

3.2 Detecting Polypharmacy

In this work, we used temporal windows and user defined thresholds to determine what would be considered as polypharmacy. Information about prescriptions obtained from the dataset go under three levels of examination by which the three types of polypharmacy can be produced. The result of each polypharmacy definition is then statistically analyzed to provide prevalence analysis. This includes studying the occurrence of single-elements (e.g., single drugs, single classes, or single active ingredients), and the co-occurrence of multiple elements of the same basic type (e.g., two-drugs, two drug classes, two active ingredients, three-drugs, three drug classes, three active ingredients, etc.). Then, we analyze the possible association between polypharmacy combinations of the three levels and ER visits. After that, we estimate the richness for all polypharmacy combinations of multiple elements of the same basic type.

Finally, we observe the thresholds of the result of each polypharmacy definition and study their association with the number of ER visits. We use the result of this analysis to propose a refined definition of polypharmacy using the three levels. Figure 3.1 shows the general workflow for our methodology.

Figure 3.1: General work flow for our methodology

Figure 3.2 shows the algorithm we used to extract polypharmacy for the three definitions.

We run the detection algorithm for all patients in the data set to generate polypharmacy sets for each patient.

```
Function detectPolypharmacy(String medications [], thresholds)
begin
  int i,j
  String Polypharmacy [], PatientPolypharmacy []
  for i=1 to maxWindow
    begin
      for j=1 to medicationLength
        begin
          if (medication[j] date > windowStart date &&< windowEnd date) then
            Polypharmacy.add(medication[j])
          end if
          j=j+1
        end
        i=i+1
      end
      if (Polypharmacy.length >= threshold) then
        patientPolypharmacy.add(Polypharmacy)
      endif
    end
  end
```

Figure 3.2: Polypharmacy detection algorithm

We used data from the NHANES dataset publicly provided by the U.S. Food and Drug Administration (FDA) to map drugs to their ingredients using National Drug Codes (NDC). Then we map drugs to their drug classes using data provided in our MEPS dataset.

First we apply the algorithm to detect drug polypharmacy. After that, we used a lookup function for retrieving the corresponding ingredients and classes. If the active ingredients were not found by drug NDC, we retry retrieving the ingredients by drug names. If no ingredients were found even after the second attempt, the drug NDC is used in the active ingredients polypharmacy. Finally, the same algorithm in Figure 3.2 is applied to count active ingredients and drug classes within each time window and identify polypharmacy groups based on the given thresholds for each type.

The output from this detection algorithm varies depending on the choice of the thresholds for each: drugs, active ingredients, and drug classes. As discussed earlier in Chapter 2, studies have used various values for these thresholds in an arbitrary manner, without a clear rational

behind their choices. In fact, determining the problematic thresholds has been considered a challenge in studying polypharmacy[12]. As a consequence, in this study we propose a new method for automating the selection of polypharmacy thresholds by studying different thresholds for each type of polypharmacy and their negative effects on patients. We used the results we obtained to drive a new way for choosing polypharmacy parameters. Next section introduces this contribution.

3.3 Automated Thresholds for Polypharmacy

According to a study by Salwe et al [18], “The single most important predictor of inappropriate prescribing and risk of adverse drug events in older patients is the number of prescribed drugs”. Polypharmacy problems can be recognized by either identifying threshold on the number of medication elements (drugs, drug classes, active ingredients) or problematic combinations of the elements. In this study, we analyze polypharmacy from both perspectives. This section illustrates our proposed method for defining polypharmacy thresholds. We studied different thresholds for the three definitions of polypharmacy and examined them against a specific measure of risk for ER visits. We varied the thresholds incrementally starting at the simplest value of 1 and then we observe how the ratio

$$ERPP(i) = \frac{\#ER(i)}{\#PP(i)}$$

changes with increasing thresholds, where $\#ER(i)$ = total number of ER visits for cluster i , while $\#PP(i)$ == total number of polypharmacy (PP) for cluster i . To estimate the change attributed to each threshold, we defined a delta function as follows:

$$\Delta(k, j) = \frac{(\frac{\#ER}{\#PP})_k - (\frac{\#ER}{\#PP})_j}{(\frac{\#ER}{\#PP})_j}$$

where k and j are two thresholds. To make this comparison more meaningful, we assume intuitively that the least value for the severity of ER problems can be attributed to threshold of value 1 (i.e., single drug, single active ingredient, or single drug class should cause the least ER problems for a given definition of polypharmacy). Based on this assumption, we consider a specific case of the delta function:

$$\Delta(k, 1) = \frac{(\frac{\#ER}{\#PP})_k - (\frac{\#ER}{\#PP})_1}{(\frac{\#ER}{\#PP})_1}$$

The percentage threshold can then be chosen by considering the variation of $\Delta(k, 1)$. A specific percentage increase of this measure can be chosen depending on the risk level that is desired to be investigated. We use 50% increase as an example here.

We calculate the values of the defined ratio $ERPP(i)$ for each threshold in each year separately and then we averaged the values for all the defined thresholds over the five MEPS years. Overall, we observed that 50% increase happens at the threshold range of 3-4 for drug polypharmacy. On the other hand, according to the values of this function, it can be observed that 50% increase in ER measure happens around thresholds 4-5 for active ingredients. With respect to drug classes, this increase happens around the thresholds value of 3-4 values for TC1 and around 5-6 for TC1S1 polypharmacy. Detailed results are presented in Chapter 4. Considering these thresholds for each polypharmacy definition leads to the idea of refining the definition of polypharmacy using these values as sub-thresholds that should be met collectively. Next section further explains this concept.

3.4 Refining Definition of Polypharmacy

The discussion in Section 3.3 leads to the idea of redefining polypharmacy using the thresholds at which a significant increase in ER problems is first observed. As a result, we propose the use of a composite approach to define polypharmacy based on the following criteria:

- Taking k_{Δ} or more drugs
- Taking $k_{\Delta I}$ or more active ingredients
- Taking $k_{\Delta c}$ or more drug classes by either definition of drug classes.

Where k_{Δ} , $k_{\Delta I}$, $k_{\Delta c}$ are thresholds for drugs, active ingredients, and drug classes respectively.

Then the definition can be specified by joint consideration of the three criteria, this include:

- Strict polypharmacy definition (Using AND Logic on the three definitions)
- Less strict polypharmacy definition (Using OR Logic on the three definitions)

The result is a polypharmacy definition that satisfies on of the following possibility: (AI here means active ingredients)

- Meeting 1 criteria of the three. i.e., the following definitions:
 - drug OR AI OR either type of drug classes
 - Drug OR AI
 - Drug OR either type of drug classes
 - AI OR either type of drug classes
- Meeting 2 criteria of the three (with at most one of the drug classes thresholds). i.e., the following definitions:

- Drug AND AI
 - Drug AND either type of drug classes
 - AI AND either type of drug classes
- Meeting all criteria of the three (with at most one of the drug classes thresholds) i.e., the following definition:
 - Drug AND AI AND either type of drug classes

We calculate the values of the ratio, $ERPP(i) = \frac{\#ER(i)}{\#PP(i)}$ for each composite definition and compare the results in Chapter 4.

The choice here could depend on the application at hand. To put this in perspective, a person taking 3 drugs that involve two active ingredients and one drug class might not be exposed to harm as much as a person taking three drugs with five active ingredients and three classes. Such discussion on thresholds and strictness of polypharmacy definition can be further enriched by physicians, pharmacologists, and health care specialists to derive more insightful conclusions. Chapter 4 exhibits a computational and comparative analysis for polypharmacy extracted from popular data using the three definitions.

3.5 Computational Analysis of the Three Definitions

In this work, we perform a computational analysis of the three different approaches to defining polypharmacy. First, we statistically analyze the prevalence of polypharmacy using different medication elements. This includes studying the occurrence of single-elements (e.g., single drugs, single classes, or single active ingredients), and the co-occurrence of multiple elements of the same basic type (e.g., two-drugs, two drug classes, two active ingredients, three-drugs, three drug classes, three active ingredients, etc.). Then, we analyze the possible association between polypharmacy combinations of the three levels and ER visits. After that, we estimate the richness for all polypharmacy combinations of multiple elements of the same basic type

3.5.1 Prevalence

Multiple variables are used to analyze the prevalence of each polypharmacy definition. They include: the average number of elements in the polypharmacy, the number of polypharmacy sets, the average number of polypharmacy per patient, the maximum thresholds found for polypharmacy sets, and the counts of occurrence and co-occurrence of multiple elements for polypharmacy. This analysis also summarizes the top polypharmacy combinations of drugs, active ingredients, and drug classes that were ranked based on the ER visits they were associated with.

3.5.2 Association of Polypharmacy with ER

In this study, we have used three measures to investigate relationships between different polypharmacy definitions and the number of emergency room visits for patients consuming those multiple drugs. We first considered the number of elements in each polypharmacy as a leading predictor for problems connected to ER visits. Thus, we clustered polypharmacy results into groups based on the number of drugs, number of active ingredients, or number of drug classes, respectively. Then we summed up the number of ER visits for every group and normalized it by the number of polypharmacy instances found in the same cluster as illustrated by the following ratio:

$$\begin{aligned} ERPP(i) &= \frac{\text{Total of ER visitis for cluster}(i)}{\text{Total number of PP in cluster } (i)} \\ &= \frac{\#ER(i)}{\#PP(i)} \end{aligned} \quad (1)$$

where (i) indicates the clusters: 1-element, 2-4 elements, 5-8 elements, 9-12 elements, and all elements >12; and PP stands for polypharmacy.

The second measure indicated the percentage that this cluster represents with respect to the total number of ER visits for the whole year. This is defined as the following rate:

$$\frac{\#ER(i)}{\text{Total } \#ER_s} = \frac{\#ER(i)}{\sum_i \#ER(i)} \quad (2)$$

Finally, we calculated the probability that a patient in cluster(i) would visit the ER using the following fraction:

- Cluster ER Probability, $ERP(i) = \frac{\#ER(i)}{\#patients(i)} = \frac{\#ER(i)}{\#PT(i)}$

Where #pt(i)= number of patients in cluster i.

$$PPER1(i) = \frac{ERP(i)}{\sum_j ERP(j)}$$

Assuming conditional independence; we can also measure the probability as follows:

- $ERP2(i) = \frac{1}{\#PT(i)} \frac{\#ER(i)}{\sum_h \#ER(h)}$

$$PPER2(i) = \frac{ERP2(i)}{\sum_h \#ERP2(h)}$$

It is important to notice that a patient can belong to multiple groups as patients would have multiple polypharmacy each of which has different number of elements. Independent of the basis

used for the polypharmacy definition, the results showed a general increase in ER problems with increasing number of drugs/drug classes/or active ingredients. Details on the results on analysis of these three measures can be found in Chapter 4.

3.5.3 Richness and Over-Representation

Besides identifying polypharmacy lists and their associations with ER admissions, we analyze the richness for each polypharmacy by which we study how the expected observation of polypharmacy in relation to its actual observation. This is defined by the following ratio:

$$\text{Richness} = \frac{\#actual\ observation}{\#expected\ observation}$$

For cases involving two elements, say A and B, this is mathematically equivalent to the following:

$$\text{Richness}(A,B) = \frac{P(A\ and\ B)}{P(A) * P(B)}$$

where A and B are drugs, active ingredients, or drug classes, and P is probability.

The probability for a single element (e) is calculated as:

$$P(e) = \frac{\#occ(e)}{\sum_j \#occ(j)}$$

Where #occ(e) = number of occurrences of element e.

While the probability for two-element and three-element polypharmacy are calculated as:

$$P(e_1\ and\ e_2) = \frac{\#occ(e_1\ and\ e_2)}{\sum_i \sum_j \#occ(e_i\ and\ e_j)}$$

(That is, the relative occurrence of this specific ($e_1\ and\ e_2$) pair, over the occurrence of all other two-element pairs that appeared in the dataset.)

$$P(e_1\ and\ e_2\ and\ e_3) = \frac{\#occ(e_1\ and\ e_2\ and\ e_3)}{\sum_i \sum_j \sum_k \#occ(e_i\ and\ e_j\ and\ e_k)}$$

Thus, for the 2-element and 3-element cases, we have:

$$Richness(e_1, e_2) = \frac{P(e_1 \text{ and } e_2)}{P(e_1) * P(e_2)}$$

$$Richness(e_1, e_2, e_3) = \frac{P(e_1 \text{ and } e_2 \text{ and } e_3)}{P(e_1) * P(e_2) * P(e_3)}$$

The significance of studying polypharmacy richness can be seen by comparing the likelihood that two or more combinations would appear together with the likelihood of its single element occurrences. For example, if drug A has high probability to appear as a single drug and drug B also has a high probability to appear as a single drug, it would be expected that the two drugs will occur as two-drug polypharmacy i.e. (the polypharmacy: drug A + drug B). The richness measure however would show whether the actual observation agrees or varies with the expected observation. In particular, higher values for richness reflect higher occurrences of the joint polypharmacy in the dataset than expected while lower values mean that the actual observation were lower than expected. We study richness of occurrence, and richness of occurrence with ER visits, for two-element and three-element polypharmacy. Chapter 4 includes richness values for the top overrepresented polypharmacy.

Chapter 4: Results

4.1 Dataset

Studying prescription claims provides essential background about prescription practices. In fact, monitoring claims was mandated for medication observation based on a recent Act made on Dec. 2016 [32]. In this work, we used prescriptions claims from the Medical Expenditure Panel Survey (MEPS) for outpatients for years 2011-2015. MEPS is a set of large-scale national household surveys for noninstitutionalized civilians (i.e., families and individuals, their medical providers, and employers) in the United States [29]. The data was collected from interviews conducted five times during their panels. The interviews are referred to as five rounds. Round dates reflect interview dates, but based on prescription dates the prescriptions were reallocated to round numbers (1-5) representing intervals of about 3 to 6 months. Thus, the temporal windows used to detect polypharmacy in our work are the predefined rounds in MEPS dataset. We extracted patient IDs, round numbers, round start and end dates, emergency room visits, as well as drug NDCs and drug names. Patient claims have already been sorted based on patients IDs by the collectors. Prescriptions that belong to one patient are consecutive within the file of the calendar year. Further details about the data can be found at the MEPS website [29].

Table 4.1 summarizes information on the MEPS datasets from (2011-2015) including the number of patients and number of prescriptions for each year.

Table 4.1: Summary of MEPS dataset characteristics

	2011	2012	2013	2014	2015	Total
#Patients	19168	20431	19966	18963	19604	98132
#Prescriptions	313748	324745	327558	319468	330454	1615973
#ER visits	240994	137318	163123	174012	172146	887593
#Panels	15-16	16-17	17-18	18-19	19-20	15-20

It is important here to state the assumptions we made while using this dataset. We assume:

- Patients take all medications they were prescribed and started the medications once they get them.
- Repeated drugs or refills within the same time window are not counted.
- ER visits extracted from MEPS files represents the total ER visits for patients within the MEPS year. In particular, there is no indication that those ER visits happened prior or later than the polypharmacy sets detected at a given round. Such information would provide a better view of polypharmacy-ER associations including polypharmacy that might have resulted from ER visits. However, the dataset did not provide such level of details about the ER visits.
- Count of single elements (i.e., drugs, active ingredients, or drug classes) is the count of elements that occurred individually in a single round for a patient, and count of combinations (i.e., two elements, or three elements) is the count of the occurrence of these combinations in a single round for a patient.

- The occurrence (#occ) of single element (i.e., drug, active ingredient, or drug class) means the times that this element appears individually in a single round for a patient while the occurrence with ER (#ER) for a single element means the sum of ER visits for the patient who was prescribed with this single element. These assumptions also apply for combinations of elements. As a result, the occurrence with ER (#ER) could be higher than the occurrence (#occ) in some cases.

Next section provides statistical information and observations about the popularity of polypharmacy defined by drugs, drug active ingredients, and drug classes.

4.2 Prevalence

The following three sections shows prevalence analysis with regard to each polypharmacy definition. It is important to point that the detection algorithm threshold was adjusted to include every polypharmacy including single-case polypharmacy (single drugs, AIs, and drug classes, we still call it polypharmacy even though they apparently may not necessarily be, as we want to use a uniform the terminology to describe the medication elements taken by patients). Also, the maximum number for each polypharmacy definition is fixed at three since this reflects the maximum number of rounds found in MEPS yearly file.

4.2.1 Prevalence of polypharmacy using number of drugs

Table 4.2 describes prevalence of polypharmacy defined by number of drugs for the MEPS dataset. It can be observed that the average number of drugs in the polypharmacy sets found by this definition were approximately around 3.3. Generally, a patient would have about 2 polypharmacy. The maximum number of drugs used concurrently by one patient (i.e., in one round) is 38 as reported in 2013. The proportion of single drugs is around 34% of all polypharmacy while it was around 19% for two-drug combinations and nearly 13% for three-drug combinations.

Table 4.2: Statistics on prevalence of polypharmacy based on number of drugs.

	2011	2012	2013	2014	2015	Total
Avg of # drugs in PP	3.251	3.240	3.363	3.484	3.482	3.365
Total number of PP for all patients	39205	41121	40130	38839	40382	199677
Avg number of PP per patient	2.045	2.012	2.009	2.048	2.059	2.035
Max # elements in PP	33	37	32	38	32	34.4 **
Max number of polypharmacy per patient	3	3	3	3	3	3
Count of single drug	13,737	14,430	13,519	12,847	13,321	67854

Count of two-drug combinations	7798	8265	7913	7613	7892	39481
Count of three-drug combinations	5062	5391	5286	4898	5138	26861

** Average value is indicated

We extracted drugs that patients take in each round. The resulting sets include combinations of single drugs, two-drugs, and three drugs, and so on. Then we summarized the results of similar drugs for different patients and different years by adding their counts. The result is a table for each possible combination with their counts in each year and collectively in all the 5 years. In our work, we only focus on the first three combinations. **Table 4.3**, **Table 4.4**, and **Table 4.5** show the top 30 polypharmacy sets of single drugs, two-drugs, and three drugs, respectively, ranked by their occurrence in every year and in total of the five years.

Table 4.3: Top 30 single-drugs in the dataset ranked by their occurrences

		Number of Occurrence					
	Single-drugs	2011	2012	2013	2014	2015	Total
1	AMOXICILLIN	931	958	857	835	890	4,471
2	AZITHROMYCIN	732	848	706	694	200	3,180
3	LISINOPRIL	309	392	348	330	358	1,737
4	LEVOTHYROXIN	290	335	326	354	390	1,695
5	IBUPROFEN	271	333	368	332	371	1,675
6	HYDROCO/APAP	282	264	236	255	201	1,238
7	SIMVASTATIN	284	246	180	156	148	1,014
8	ALBUTEROL	156	207	149	142	131	785
9	METFORMIN	166	174	146	134	160	780
10	OMEPRAZOLE	101	152	145	140	183	721
11	METHYLPHENID	42	145	146	178	187	698
12	AMLODIPINE	114	136	127	114	193	684
13	AMPHETAMINE	91	103	121	158	153	626
14	APAP/CODEINE	138	139	149	106	82	614
15	ATORVASTATIN	1	92	128	141	194	556
16	SERTRALINE	74	118	118	114	115	539
17	LISINOP/HCTZ	90	115	130	87	117	539
18	CEPHALEXIN	109	101	123	115	90	538
19	SYNTHROID	122	120	99	92	104	537
20	VYVANSE	114	95	112	109	102	532
21	NAPROXEN	88	101	117	90	97	493
22	AMOX/K CLAV		90	100	82	213	485
23	FLUTICASONE	77	98	104	105	83	467
24	HYDROCHLOROT	78	98	79	102	106	463
25	PROAIR HFA		101	110	111	128	450
26	CITALOPRAM	111	116	90	59	74	450

27	ATENOLOL	124	111	81	73	58	447
28	PREDNISONE	89	92	87	97	71	436
29	FLUOXETINE	76	81	79	65	71	372
30	RANITIDINE	68	70	60	63	66	327

The most common drugs prescribed within 5 MEPS years from 2011-2015 are AMOXICILLIN and **AZITHROMYCIN** which are two common antibiotics. **HYDROCO/APAP**, **IBUPROFEN** and **APAP/CODEINE** are known as strong pain killers that require monitoring by clinicians for usage and dosage.

Table 4.4: Top 30 two-drug polypharmacy ranked by their occurrences

	Two-drugs	Number of Occurrence					Total
		2011	2012	2013	2014	2015	
1	AMOXICILLIN--IBUPROFEN	39	52	66	52	85	294
2	LISINOPRIL--SIMVASTATIN	52	40	47	49	33	221
3	HYDROCO/APAP--IBUPROFEN	33	38	23	55	27	176
4	LISINOPRIL--METFORMIN	28	34	33	31	34	160
5	HYDROCHLOROT--LISINOPRIL	26	35	24	37	37	159
6	AMOXICILLIN--HYDROCO/APAP	23	31	33	40	30	157
7	AMLODIPINE--LISINOPRIL	23	18	29	34	39	143
8	AZITHROMYCIN--IBUPROFEN	26	29	26	31	8	120
9	APAP/CODEINE--AZITHROMYCIN	28	34	29	24	1	116
10	METFORMIN--SIMVASTATIN	21	22	23	15	23	104
11	AMOXICILLIN--AZITHROMYCIN	21	17	23	22	13	96
12	AMLODIPINE--HYDROCHLOROT	11	22	20	16	27	96
13	LISINOPRIL--PRAVASTATIN	21	22	28	16	9	96
14	LEVOTHYROXIN--LISINOPRIL	16	21	12	21	22	92
15	GLIPIZIDE--METFORMIN	19	15	13	21	21	89
16	ALBUTEROL--AMOXICILLIN	15	21	16	17	15	84
17	AZITHROMYCIN--HYDROCO/APAP	21	19	17	23	3	83
18	CYCLOBENZAPR--IBUPROFEN	9	18	21	18	16	82
19	CYCLOBENZAPR--HYDROCO/APAP	16	13	7	23	18	77
20	ATORVASTATIN--LISINOPRIL		9	18	20	28	75
21	LISINOPRIL--OMEPRAZOLE	7	13	8	17	25	70
22	IBUPROFEN--OXYCOD/APAP	14	8	14	18	13	67
23	CYCLOBENZAPR--NAPROXEN	10	12	19	13	12	66
24	AMLODIPINE--LISINOP/HCTZ	6	9	13	23	14	65
25	AZITHROMYCIN--PREDNISONE	11	13	16	14	9	63
26	AMOXICILLIN--APAP/CODEINE	12	18	17	5	11	63
27	ALBUTEROL--AZITHROMYCIN	24	12	11	8	4	59
28	LEVOTHYROXIN--SIMVASTATIN	7	14	16	9	13	59
29	HYDROCHLOROT--SIMVASTATIN	12	12	11	11	13	59
30	LISINOP/HCTZ--SIMVASTATIN	13	15	18	10	2	58

Considering the single-occurrences in Table 4.3 and the co-occurrences of pairs in Table 4.4, we can observe that among the most common drugs are AMOXICILLIN which occurred 4,471 times and IBUPROFEN which occurred 1,675 times. However, the pair (**AMOXICILLIN--IBUPROFEN**) occurred much less with occurrence total of 294. This indicates that the cooccurrence of two drugs in a polypharmacy does not necessarily align with the occurrence of the individual drugs involved in that polypharmacy. However, in this particular case, the pair (**AMOXICILLIN--IBUPROFEN**) was the highest occurring two-drug polypharmacy.

Table 4.5: Top 30 three-drug polypharmacy ranked by their occurrences

	Three-drugs	Number of Occurrence					Total
		2011	2012	2013	2014	2015	
1	LISINOPRIL--METFORMIN--SIMVASTATIN	12	10	10	12	12	56
2	ATORVASTATIN--LISINOPRIL--METFORMIN		6	8	12	11	37
3	LISINOPRIL--METFORMIN--PRAVASTATIN	5	7	4	3	16	35
4	GLIPIZIDE--LISINOPRIL--METFORMIN	6	13	5	4	5	33
5	HYDROCHLOROT--LISINOPRIL--SIMVASTATIN	4	9	6	8	3	30
6	CYCLOBENZAPR--HYDROCO/APAP--IBUPROFEN	6	7	6	4	6	29
7	LISINOPRIL--LOVASTATIN--METFORMIN	3	6	1	8	6	24
8	AMOXICILLIN--HYDROCO/APAP--IBUPROFEN	4	2	6	4	4	20
9	HYDROCHLOROT--LISINOPRIL--METFORMIN	4	3	1	7	5	20
10	AMLODIPINE--HYDROCHLOROT--LISINOPRIL	3	6	8	2	1	20
11	GLYBURIDE--LISINOPRIL--METFORMIN	3	7	6		1	17
12	LISINOPRIL--METOPROLOL--SIMVASTATIN	6	4	3	4		17
13	AMLODIPINE--LISINOPRIL--SIMVASTATIN	4	7	1	1	2	15
14	HYDROCHLOROT--LISINOPRIL--PRAVASTATIN	2	6	4	2		14
15	LEVOTHYROXIN--SIMVASTATIN--TRIAMT/HCTZ	2	4	2	3	2	13
16	LEVOTHYROXIN--LISINOPRIL--SIMVASTATIN	2	1		5	5	13
17	AMLODIPINE--LEVOTHYROXIN--SIMVASTATIN	2	5		3	3	13
18	GLIMEPIRIDE--LISINOPRIL--METFORMIN	2	1	3	3	4	13
19	ATENOLOL--HYDROCHLOROT--SIMVASTATIN	3	5	5			13
20	LEVOTHYROXIN--LISINOPRIL--PRAVASTATIN		4	2	4	2	12
21	AMLODIPINE--METOPROLOL TAR--SIMVASTATIN		4	4	3	1	12
22	LISINOPRIL--METOPROLOL TAR--SIMVASTATIN		5		4	3	12
23	CARVEDILOL--LISINOPRIL--PRAVASTATIN	4	5	2	1		12
24	ATORVASTATIN--LISINOPRIL--METOPROLOL TAR		1	3	3	5	12
25	ALBUTEROL--AZITHROMYCIN--PREDNISOLONE	3	4	1	2	1	11
26	ALBUTEROL--AZITHROMYCIN--PREDNISONE	2	5	2	2		11
27	GLIPIZIDE--METFORMIN--PRAVASTATIN	4	3	1	2	1	11
28	LISINOP/HCTZ--METFORMIN--SIMVASTATIN	3		1	4	3	11
29	LEVOTHYROXIN--LISINOPRIL--METFORMIN	1		5		4	10
30	CYCLOBENZAPR--HYDROCO/APAP--NAPROXEN		4	4	1	1	10

From Table 4.3, Table 4.4, and Table 4.5 we can see that the occurrence values decrease with the increase in number of drugs (i.e, single-drugs have highest occurrences value followed by two-drugs, followed by three-drugs, and this persists even for combinations containing more than three drugs).

4.2.2 Prevalence of polypharmacy using number of active ingredients

Table 4.6 describes the prevalence of polypharmacy using the number of drug active ingredients which was obtained from MEPS five calendar years (2011-2105). As shown in the table, the average number of active ingredients in the polypharmacy sets found by this definition were approximately around 3.7. On average, a patient would have 2.035 cases of polypharmacy. The maximum number of active ingredients used concurrently by one patient (i.e., in one round) is 41 as reported in 2014. The proportion of single active ingredients is about 29% of all polypharmacy while it is nearly 18% for two-active ingredient combinations and around 13% for three-active ingredient combinations.

Table 4.6: Statistics on Prevalence of Polypharmacy using number of active ingredients

	2011	2012	2013	2014	2015	Total
Avg of # AIs in PP	3.626	3.604	3.712	3.859	3.845	3.730
Total number of PP for all patients	39205	41120	40130	38839	40382	199676
Avg number of PP per patient	2.045	2.012	2.009	2.048	2.059	2.035
Max # elements in PP	35	37	32	41	38	36.6**
Max number of polypharmacy per patient	3	3	3	3	3	3
Count of single AI	11,964	12,631	11,798	11,258	11,342	58,993
Count of two-AI combinations	7578	7872	7655	7148	7587	37840
Count of three-AI combinations	5235	5679	5495	5105	5398	26912

** Average value is indicated

Tables 4.7, 4.8, and 4.9, respectively, show the top 30 polypharmacy sets for single active ingredients, two- active ingredients, and three active ingredients ranked by occurrence. We can observe that the two-active ingredients (namely, **SULFAMETHOXAZOLE** and **TRIMETHOPRIM**) in the top rank for case of two-active ingredients did not even appear in the top 30 ranks for case of single active ingredient prevalence. Similarly, the active ingredient **SALMETEROL XINAFOATE** which appeared in the top 3-active ingredients did not appear in the top 30 ranks for single active ingredients.

Table 4.7: Top 30 single-ingredients polypharmacy ranked by their occurrences.

	Single-ingredients	Number of Occurrence					Total
		2011	2012	2013	2014	2015	
1	AMOXICILLIN	945	962	863	836	899	4,505
2	AZITHROMYCIN DIHYDRATE	744	869	717	699	204	3,233
3	LEVOTHYROXINE SODIUM	457	504	457	459	516	2,393
4	ALBUTEROL SULFATE	307	402	416	355	395	1,875
5	LISINOPRIL	309	392	348	330	358	1,737
6	IBUPROFEN	283	337	371	333	372	1,696
7	SIMVASTATIN	292	246	180	156	148	1,022
8	METHYLPHENIDATE HYDROCHLORIDE	158	202	173	190	207	930
9	METFORMIN HYDROCHLORIDE	168	178	151	138	167	802
10	OMEPRAZOLE	103	153	145	140	185	726
11	AMLODIPINE BESYLATE	129	140	131	121	201	722
12	FLUTICASONE PROPIONATE	103	144	150	126	104	627
13	SERTRALINE HYDROCHLORIDE	99	129	125	124	126	603
14	CEPHALEXIN	115	107	126	115	90	553
15	LISDEXAMFETAMINE DIMESYLATE	116	95	112	109	102	534
16	HYDROCHLOROTHIAZIDE	106	109	90	109	113	527
17	NAPROXEN	89	101	120	91	98	499
18	CITALOPRAM HYDROBROMIDE	112	117	91	60	79	459
19	MONTELUKAST SODIUM	97	100	91	85	79	452
20	ATENOLOL	124	111	81	73	58	447
21	PREDNISONE	89	92	88	98	71	438
22	ATORVASTATIN CALCIUM TRIHYDRATE	117	103	35	92	79	426
23	METOPROLOL TARTRATE	103	97	69	75	79	423
24	FLUOXETINE HYDROCHLORIDE	81	90	89	71	73	404
25	LORATADINE	78	76	56	66	74	350
26	RANITIDINE HYDROCHLORIDE	73	74	60	69	67	343
27	CETIRIZINE HYDROCHLORIDE	58	54	66	85	72	335
28	PENICILLIN V POTASSIUM	63	52	71	79	63	328
29	OSELTAMIVIR PHOSPHATE	41	46	86	79	62	314
30	555904358 **	138	33	33	96	14	314

**Drug NDC is used when no active ingredients cannot be found.

Table 4.8: Top 30 two-active ingredient polypharmacy ranked by their occurrences

	Two-ingredients	Number of Occurrence					Total
		2011	2012	2013	2014	2015	
1	ACETAMINOPHEN--HYDROCODONE BITARTRATE	216	192	199	285	227	1119
2	HYDROCHLOROTHIAZIDE--LISINOPRIL	120	157	172	127	159	735
3	AMOXICILLIN--CLAVULANATE POTASSIUM	118	113	126	103	218	678
4	ACETAMINOPHEN--CODEINE PHOSPHATE	147	146	146	107	86	632
5	SULFAMETHOXAZOLE--TRIMETHOPRIM	71	98	71	76	192	508
6	ACETAMINOPHEN--OXYCODONE HYDROCHLORIDE	107	86	74	67	106	440
7	ETHINYL ESTRADIOL--NORETHINDRONE ACETATE	59	67	55	61	69	311
8	AMOXICILLIN--IBUPROFEN	45	52	67	52	85	301
9	ETONOGESTREL--ETHINYL ESTRADIOL	62	52	53	38	43	248
10	HYDROCHLOROTHIAZIDE--LOSARTAN POTASSIUM	26	52	41	47	69	235
11	LISINOPRIL--SIMVASTATIN	53	40	47	49	33	222
12	FLUTICASONE PROPIONATE--SALMETEROL XINAFOATE	61	45	34	25	54	219
13	ALBUTEROL SULFATE--FLUTICASONE PROPIONATE	37	49	34	36	34	190
14	AMLODIPINE BESYLATE--BENAZEPRIL HYDROCHLORIDE	44	42	26	35	34	181
15	BISOPROLOL FUMARATE--HYDROCHLOROTHIAZIDE	77	67	10	7	10	171
16	LISINOPRIL--METFORMIN HYDROCHLORIDE	31	33	33	31	35	163
17	AMLODIPINE BESYLATE--LISINOPRIL	23	19	29	36	40	147
18	ATENOLOL--CHLORTHALIDONE	44	40	30	23	8	145
19	ALBUTEROL SULFATE--MONTELUKAST SODIUM	37	26	31	22	22	138
20	HYDROCHLOROTHIAZIDE--PROPRANOLOL HYDROCHLORIDE	1	2	68	61		132
21	HYDROCHLOROTHIAZIDE--TRIAMTERENE	24	27	14	28	33	126
22	AZITHROMYCIN DIHYDRATE--IBUPROFEN	26	30	27	31	8	122
23	AMLODIPINE BESYLATE--HYDROCHLOROTHIAZIDE	16	23	24	20	30	113
24	METFORMIN HYDROCHLORIDE--SIMVASTATIN	21	24	26	15	23	109
25	ALBUTEROL SULFATE--BECLOMETHASONE DIPROPIONATE	18	30	32	11	13	104
26	HYDROCHLOROTHIAZIDE--VALSARTAN	30	32	12	11	19	104
27	AMOXICILLIN--ALBUTEROL SULFATE	20	23	17	20	23	103
28	GLIPIZIDE--METFORMIN HYDROCHLORIDE	25	16	15	23	22	101
29	ALBUTEROL SULFATE--BUDESONIDE	22	21	18	22	17	100
30	CYCLOBENZAPRINE HYDROCHLORIDE--IBUPROFEN	16	19	26	19	18	98

Table 4.9: Top 30 three-active ingredient polypharmacy ranked by their occurrences

	Three-ingredients	Number of Occurrence					Total
		2011	2012	2013	2014	2015	
1	ALBUTEROL SULFATE--FLUTICASONE PROPIONATE--SALMETEROL XINAFOATE	40	38	38	25	24	165
2	ACETAMINOPHEN--HYDROCODONE BITARTRATE--IBUPROFEN	24	30	28	53	28	163
3	BROMPHENIRAMINE MALEATE--DEXTROMETHORPHAN HYDROBROMIDE--PSEUDOEPHEDRINE HYDROCHLORIDE	13	29	47	27	39	155
4	HYDROCORTISONE--NEOMYCIN SULFATE--POLYMYXIN B SULFATE	23	24	34	25	17	123
5	AMLODIPINE BESYLATE--HYDROCHLOROTHIAZIDE--LISINOPRIL	11	17	25	31	17	101
6	HYDROCHLOROTHIAZIDE--LISINOPRIL--SIMVASTATIN	20	25	25	18	5	93
7	AMOXICILLIN--ACETAMINOPHEN--HYDROCODONE BITARTRATE	12	10	14	37	18	91
8	ACETAMINOPHEN--IBUPROFEN--OXYCODONE HYDROCHLORIDE	15	11	19	20	16	81
9	ACETAMINOPHEN--CYCLOBENZAPRINE HYDROCHLORIDE--HYDROCODONE BITARTRATE	16	11	9	22	18	76
10	AZITHROMYCIN DIHYDRATE--ACETAMINOPHEN--CODEINE PHOSPHATE	19	18	20	14	1	72
11	AMLODIPINE BESYLATE--HYDROCHLOROTHIAZIDE--LOSARTAN POTASSIUM	9	10	19	12	20	70
12	ACETAMINOPHEN--BUTALBITAL--CAFFEINE	10	16	11	16	10	63
13	LISINOPRIL--METFORMIN HYDROCHLORIDE--SIMVASTATIN	12	10	14	13	13	62
14	ACETAMINOPHEN--HYDROCODONE BITARTRATE--OXYCODONE HYDROCHLORIDE	8	11	8	15	13	55
15	ACETAMINOPHEN--HYDROCODONE BITARTRATE--PENICILLIN V POTASSIUM	11	4	12	20	8	55
16	ACETAMINOPHEN--CODEINE PHOSPHATE--IBUPROFEN	9	9	9	11	12	50
17	HYDROCHLOROTHIAZIDE--LISINOPRIL--METFORMIN HYDROCHLORIDE	11	11	4	12	12	50
18	ACETAMINOPHEN--AMOXICILLIN--HYDROCODONE BITARTRATE	8	8	11	8	14	49
19	ACETAMINOPHEN--AZITHROMYCIN DIHYDRATE--CODEINE PHOSPHATE	10	15	10	14		49
20	AMOXICILLIN--ACETAMINOPHEN--CODEINE PHOSPHATE	7	13	14	4	11	49
21	ACETAMINOPHEN--CEPHALEXIN--HYDROCODONE BITARTRATE	15	6	8	16	3	48
22	AZITHROMYCIN DIHYDRATE--ACETAMINOPHEN--HYDROCODONE BITARTRATE	10	10	8	18	1	47
23	ALBUTEROL SULFATE--FLUTICASONE PROPIONATE--MONTELUKAST SODIUM	13	6	15	9	3	46

24	HYDROCHLOROTHIAZIDE--LISINOPRIL--PRAVASTATIN SODIUM	10	12	11	5	4	42
25	AZITHROMYCIN DIHYDRATE--CODEINE PHOSPHATE--GUAIFENESIN	7	19	5	3	7	41
26	GLIPIZIDE--LISINOPRIL--METFORMIN HYDROCHLORIDE	10	14	8	4	5	41
27	BROMPHENIRAMINE MALEATE--DEXTROMETHORPHAN HYDROBROMIDE--PHENYLEPHRINE HYDROCHLORIDE	9	5	20	4	2	40
28	LISINOPRIL--METOPROLOL TARTRATE--SIMVASTATIN	15	9	3	8	4	39
29	HYDROCHLOROTHIAZIDE--LISINOPRIL--METOPROLOL TARTRATE	3	5	6	10	13	37
30	LISINOPRIL-- METFORMIN HYDROCHLORIDE#PRAVASTATIN SODIUM	5	7	4	3	16	35

It can be seen from the three Tables 4.7, 4.8, and 4.9 that some active ingredients names are similar to the original drugs. This is because some drugs have only one active ingredient and so are named based on the substance. Many drugs can share the exact sets of active ingredients or subsets of them. As a consequence, the occurrences of single or multiple active ingredients may be originated from different drugs. Table 4.10 shows some instances of active ingredients matched with the drugs they compose.

Table 4.10: List of ingredients/substances matched with their parent drugs.

Substance name	Drugs Name
ZOLEDRONIC ACID	Reclast Zometa
ZOLPIDEM TARTRATE	Ambien CR Edluar Intermezzo ZolpiMIST
BRIMONIDINE TARTRATE	Brimonidine Tartrate Ophthalmic Solution, 0.2% LUMIFY Redness Reliever Eye Drops Mirvaso ALPHAGAN P
ADAPALENE--BENZOYL PEROXIDE	epiduo forte EPIDUO ADAPALENE and BENZOYL PEROXIDE Adapalene and Benzoyl Peroxide adapalene and benzoyl peroxide

BROMPHENIRAMINE MALEATE -- PSEUDOEPHEDRINE HYDROCHLORIDE	RYNEX PSE RYNEX PE Q-Tapp Lodrane D Brotapp Walgreens Fast Acting Heartburn Relief Extra Strength
ALUMINUM HYDROXIDE -- MAGNESIUM CARBONATE	SohMed Acid Reducer RIGINIC ANTACID LIQUID GOOD NEIGHBOR PHARMACY Antacid Extra Strength GAVISCON Gaviscon GAVIS-CARE ANTACID Foamcoat Antacid FAST ACTING Heartburn Relief EXTRA STRENGTH HEARTBURN RELIEF ANTACID EXTRA STRENGTH HEARTBURN RELIEF equate Extra Strength Antacid CVS Health Extra Strength Heartburn Relief Antacid Aluminum hydroxide and Magnesium carbonate ACID GONE ANTACID Acid Gone Antacid
PANCRELIPASE LIPASE --PANCRELIPASE PROTEASE --PANCRELIPASE AMYLASE	Viokace ZENPEP ULTRESA PANCRELIPASE Creon
CODEINE PHOSPHATE -- GUAIFENESIN -- PSEUDOEPHEDRINE HYDROCHLORIDE	Ceditussin DAC LORTUSS Tricode Tusnel Virtussin DAC

BROMPHENIRAMINE MALEATE	BIO Dtuss
--	BROMPHENIRAMINE MALEATE, PSEUDOEPHEDRINE HYDROCHLORIDE, AND DEXTROMETHORPHAN HYDROBROMIDE
DEXTROMETHORPHAN HYDROBROMIDE	
--	Q Tapp Cold and Cough
PSEUDOEPHEDRINE HYDROCHLORIDE	

From Table 4.10 we can see that many drugs that share the same active ingredient(s) have the same name but with some minor changes e.g., different upper vs. lower case, OR shorter vs. longer names. This has been handled by our algorithm by converting all drug names to lower case before performing the lookup function. If the drug at hand was not found using the lookup function and its name, we run the lookup function for the second time using drug NDC.

Using active ingredients approach reveals information about the substances that occurred frequently regardless of their parent drugs. For example, **LORATADINE** is an active substance for allergy medications. According to our statistics, **LORATADINE** was ranked 25 based on the occurrence of active ingredients and 40 based on the total of ER visits even though the allergy relief drugs are not ranked high considering ER visits. Also, the substance: **HYDROCHLOROTHIAZIDE** (ranked 22 by ER) is an active ingredient found in a lot of drugs, which may make observing its patterns prioritized for health care people. Some examples of pairs and triples that include **HYDROCHLOROTHIAZIDE** are:

- HYDROCHLOROTHIAZIDE--LOSARTAN POTASSIUM
- HYDROCHLOROTHIAZIDE--LISINOPRIL
- AMLODIPINE BESYLATE--HYDROCHLOROTHIAZIDE
- HYDROCHLOROTHIAZIDE--PROPRANOLOL HYDROCHLORIDE
- HYDROCHLOROTHIAZIDE--VALSARTAN
- BISOPROLOL FUMARATE--HYDROCHLOROTHIAZIDE
- ATENOLOL--HYDROCHLOROTHIAZIDE
- BENAZEPRIL HYDROCHLORIDE--HYDROCHLOROTHIAZIDE
- HYDROCHLOROTHIAZIDE--LEVOTHYROXINE SODIUM
- HYDROCHLOROTHIAZIDE--TEMAZEPAM
- HYDROCHLOROTHIAZIDE--TRIAMTERENE
- HYDROCHLOROTHIAZIDE--NAPROXEN
- CARBAMAZEPINE--HYDROCHLOROTHIAZIDE
- HYDROCHLOROTHIAZIDE--METFORMIN HYDROCHLORIDE
- TAMLODIPINE BESYLATE--HYDROCHLOROTHIAZIDE--LOSARTAN POTASSIUM
- ATORVASTATIN CALCIUM TRIHYDRATE--HYDROCHLOROTHIAZIDE
- ATENOLOL--CARISOPRODOL--HYDROCHLOROTHIAZIDE
- AMLODIPINE BESYLATE--HYDROCHLOROTHIAZIDE--LISINOPRIL
- EZETIMIBE--HYDROCHLOROTHIAZIDE--OLMESARTAN MEDOXOMIL
- AMOXICILLIN--HYDROCHLOROTHIAZIDE--LISINOPRIL

- HYDROCHLOROTHIAZIDE--LISINOPRIL--METOPROLOL TARTRATE
- AMLODIPINE BESYLATE--HYDROCHLOROTHIAZIDE--METOPROLOL TARTRATE

4.2.3 Prevalence using number of drug classes

Table 4.11 shows some statistics on of polypharmacy based on drug classes extracted from MEPS five years (2011-2105). Overall, the averages for number of TC1 class polypharmacy is around 2.3 while it is between 2.9 and 3 for TC1S1. The mean number of polypharmacy per patient is 2 for both types of classes. The highest number for TC1 polypharmacy elements is 13 classes. For TC1S1, there are 26 classes at most. The proportion of TCI single classes is almost 40% of all polypharmacy whereas it is almost 36% for TC1S1 class definition. Approximately 23% out of all polypharmacy sets are for the polypharmacy of two-TC1 classes and 19% for the polypharmacy of two-TC1S1 classes. Finally, the polypharmacy of combinations of three TC1 class is around 14% all polypharmacy while it is equal to 13% for the TC1S1 type.

Tables 4.12-4.14 show the top 30 polypharmacy sets of (single classes, two- classes, and three classes) ranked by occurrence, using TC1 drug classes.

Table 4.11: Prevalence of polypharmacy using number of drug classes

TC1 class	2011	2012	2013	2014	2015	Total
Avg of TC1 classes in PP	2.298	2.280	2.356	2.414	2.422	2.354
Number of PP for all patients	39205	41121	40130	38839	40382	199677
Avg number of PP per patient	2.045	2.013	2.010	2.048	2.060	2.035
Max number of elements in PP	13	12	13	13	13	12.8
Max number of polypharmacy per patient	3	3	3	3	3	3
Count of single TC1 classes	16,467	16,710	15,742	15,546	15,345	79,810
Count of two- TC1 Classes	9,674	9,887	9,370	9,309	9,432	47,672
Count of three-TC1 classes	5,663	5,550	5,727	5,781	5,623	28,344
TC1S1 class	2011	2012	2013	2014	2015	Total
Avg of TC1S1 classes in PP	2.914	2.891	3.006	3.096	3.105	3.002
Number of PP for all patients	39205	41121	40130	38839	40382	199677
Avg number of PP per patient	2.045	2.013	2.010	2.048	2.060	2.035
Max number of elements in PP	23	23	24	26	23	23.8
Max number of polypharmacy per patient	3	3	3	3	3	3
Count of single TC1S1 classes	14,641	15,441	14,451	13,778	13,569	71,880
Count of two-TC1S1 classes	7,811	8,289	7,831	7,465	7,514	38,910
Count of three- TC1S1 Classes	5189	5473	5439	5136	5062	26299

Table 4.12: Single TC1-class polypharmacy ranked by their occurrences

		Number of Occurrence					
	Single TC1-Classes	2011	2012	2013	2014	2015	Total
1	Central nervous system agents	3,329	3,440	3,386	3,583	3,422	17,160
2	Anti-infectives	2,880	2,874	2,743	2,667	2,331	13,495
3	Cardiovascular agents	2,257	2,326	2,116	2,051	2,133	10,883
4	Hormones/hormone modifiers	1,851	1,867	1,737	1,707	1,625	8,787
5	Topical agents	1,276	1,270	1,288	1,280	1,474	6,588
6	Respiratory agents	1,403	1,373	1,338	1,128	1,165	6,407
7	Metabolic agents	1,377	1,313	1,079	1,042	1,103	5,914
8	Psychotherapeutic agents	679	744	674	620	662	3,379
9	Gastrointestinal agents	512	569	473	482	525	2,561
10	Nutritional products	447	444	459	482	426	2,258
11	Antineoplastics	99	109	94	100	118	520
12	Miscellaneous agents	82	104	77	84	77	424
13	Coagulation modifiers	91	71	45	68	57	332
14	Genitourinary tract agents	48	38	34	27	25	172
15	Immunologic agents	17	32	30	34	24	137
16	Alternative medicines	7	9	14	15	12	57
17	Biologicals	2	1			1	4
	Grand Total	16,467	16,710	15,742	15,546	15,345	79,810

The **central nervous system** agents have the highest occurrence for drug classification TC1. These include narcotic analgesics (pain relievers), nonnarcotic analgesics (such as acetaminophen and NSAIDs), and sedatives.

Table 4.13: Top 30 two TC1-class polypharmacy ranked by their occurrences

		Number of Occurrence					
	Two-TC1 Classes	2011	2012	2013	2014	2015	Total
1	Cardiovascular agents--Metabolic agents	1,771	1,850	1,624	1,484	1,495	8,224
2	Anti-infectives--Central nervous system agents	718	775	761	781	727	3,762
3	Central nervous system agents--Psychotherapeutic agents	626	613	545	675	613	3,072
4	Anti-infectives --Respiratory agents	443	387	385	348	330	1,893
5	Anti-infectives--Topical agents	369	375	395	350	311	1,800
6	Central nervous system agents--Cardiovascular agents	328	340	305	353	337	1,663
7	Central nervous system agents--Hormones/hormone modifiers	287	299	236	309	330	1,461
8	Cardiovascular agents--Central nervous system agents	236	292	277	294	281	1,380
9	Cardiovascular agents--Hormones/hormone modifiers	287	292	233	241	282	1,335
10	Central nervous system agents--Respiratory agents	276	306	264	210	219	1,275
11	Respiratory agents--Topical agents	250	225	258	219	245	1,197
12	Central nervous system agents--Metabolic agents	279	234	238	219	226	1,196
13	Central nervous system agents--Topical agents	210	199	222	204	276	1,111
14	Central nervous system agents--Gastrointestinal agents	200	202	218	240	231	1,091
15	Anti-infectives--Hormones/hormone modifiers	217	205	215	213	225	1,075
16	Hormones/hormone modifiers--Respiratory agents	179	170	169	173	144	835
17	Cardiovascular agents--Gastrointestinal agents	156	170	152	176	176	830
18	Cardiovascular agents--Psychotherapeutic agents	140	169	152	130	161	752
19	Anti-infectives--Cardiovascular agents	139	151	140	162	144	736
20	Cardiovascular agents--Topical agents	143	108	114	123	163	651
21	Hormones/hormone modifiers--Topical agents	108	137	115	129	142	631
22	Hormones/hormone modifiers--Metabolic agents	119	148	126	100	125	618
23	Central nervous system agents--Nutritional products	105	121	139	127	110	602
24	Hormones/hormone modifiers--Psychotherapeutic agents	145	125	98	103	106	577

25	Cardiovascular agents--Respiratory agents	99	90	117	90	108	504
26	Cardiovascular agents--Nutritional products	95	99	108	102	97	501
27	Gastrointestinal agents--Metabolic agents	85	88	90	75	101	439
28	Metabolic agents --Psychotherapeutic agents	75	78	90	68	67	378
29	Metabolic agents --Topical agents	78	77	67	66	76	364
30	Anti-infectives-Metabolic agents	85	67	76	61	58	347

The most common class pair using TC1 classification is (**Cardiovascular agents- Metabolic agents**). Cardiovascular agents are used to treat medical conditions for heart or the circulatory system (blood vessels). Some instances are arrhythmias, blood clots, coronary artery disease, high or low blood pressure, high cholesterol, heart failure, and stroke. Metabolic agents are used to treat metabolic disorders. These disorders are defects of metabolism which occur when the body is not able to properly process fats, proteins, sugars, or nucleic acids.

Table 4.14: Top 30 three TC1-class polypharmacy ranked by their occurrences

		Number of Occurrence					
	Three-TC1 Classes	2011	2012	2013	2014	2015	Total
1	Cardiovascular agents--Central nervous system agents-- Metabolic agents	290	282	226	285	293	1376
2	Cardiovascular agents--Hormones/hormone modifiers-- Metabolic agents	241	261	241	203	213	1159
3	Central nervous system agents--Cardiovascular agents-- Metabolic agents	226	254	212	253	212	1157
4	Cardiovascular agents--Gastrointestinal agents--Metabolic agents	206	204	214	194	220	1038
5	Cardiovascular agents-- Metabolic agents -- Topical agents	127	134	115	150	126	652
6	Central nervous system agents--Cardiovascular agents--Psychotherapeutic agents	117	123	110	141	157	648
7	Cardiovascular agents-- Metabolic agents -- Nutritional products	138	118	130	133	103	622
8	Cardiovascular agents-- Metabolic agents -- Psychotherapeutic agents	115	128	120	94	110	567
9	Anti-infectives--Central nervous system agents--Respiratory agents	129	87	138	104	82	540
10	Cardiovascular agents--Coagulation modifiers--Metabolic agents	114	122	100	108	81	525
11	Anti-infectives--Cardiovascular agents--Metabolic agents	96	102	114	105	73	490
12	Anti-infectives--Central nervous system agents--Topical agents	87	77	108	98	119	489
13	Anti-infectives--Hormones/hormone modifiers--Respiratory agents	104	100	77	108	84	473

14	Central nervous system agents-- Hormones/hormone modifiers-- Psychotherapeutic agents	86	109	99	85	94	473
15	Anti-infectives--Respiratory agents--Topical agents	88	78	107	84	88	445
16	Anti-infectives--Central nervous system agents-- Hormones/hormone modifiers	97	78	86	84	94	439
17	Anti-infectives--Central nervous system agents-- Psychotherapeutic agents	83	71	88	83	84	409
18	Cardiovascular agents--Central nervous system agents--Psychotherapeutic agents	80	84	65	82	75	386
19	Cardiovascular agents-- Metabolic agents -- Respiratory agents	91	63	65	71	92	382
20	Coagulation modifiers--Cardiovascular agents-- Metabolic agents	85	82	74	63	71	375
21	Central nervous system agents-- Metabolic agents--Psychotherapeutic agents	52	73	60	83	51	319
22	Central nervous system agents--Respiratory agents--Topical agents	59	62	65	66	58	310
23	Central nervous system agents--Gastrointestinal agents--Psychotherapeutic agents	53	61	69	62	62	307
24	Central nervous system agents--Cardiovascular agents--Gastrointestinal agents	48	57	61	73	66	305
25	Anti-infectives--Central nervous system agents-- Cardiovascular agents	55	57	59	66	46	283
26	Anti-infectives--Central nervous system agents-- Gastrointestinal agents	40	39	70	58	75	282
27	Central nervous system agents-- Psychotherapeutic agents--Respiratory agents	57	35	62	64	53	271
28	Central nervous system agents--Cardiovascular agents--Hormones/hormone modifiers	47	47	48	49	52	243
29	Anti-infectives-Hormones/hormone modifiers- Topical agents	45	48	50	37	55	235
30	Cardiovascular agents-Central nervous system agents-Gastrointestinal agents	48	40	66	42	32	228

As indicated earlier in Chapter 3, using drug classes will provide less specific information on the association with health problems. This could be seen by observing **Table 4.12** that lists all single TC1-class polypharmacy ranked by their occurrences, and **Table 7 (in Appendix A)** that lists of all single TC1-class polypharmacy ranked by the corresponding ER visits. Even though the latter is a ranking based on a health problem, the order for these two tables were quite similar. This could be misleading since drugs in the same class work on multiple targets and thus we emphasize that using drugs or active ingredients provide a more accurate approaches to define polypharmacy. Next Tables 4.15 - 4.17 include the top 30 single TC1S1-classes, as well as the pairs and triples defined using TC1S1 approach.

Table 4.15: Top 30 single TC1S1-classes in the dataset ranked by their occurrences

	Single TC1S1 Classes	Number of Occurrence					Total
		2011	2012	2013	2014	2015	
1	ANALGESICS	1,652	1,773	1,759	1,722	1,613	8,519
2	PENICILLINS	1,168	1,151	1,090	1,034	1,150	5,593
3	SEX_HORMONES	1,072	1,102	994	905	872	4,945
4	MACROLIDE_DERIVATIVES	781	901	742	716	217	3,357
5	DERMATOLOGICAL_AGENTS	644	641	620	619	802	3,326
6	CNS_STIMULANTS	557	586	562	635	619	2,959
7	ANTIHYPERLIPIDEMIC_AGENTS	721	646	525	498	541	2,931
8	ANTIDEPRESSANTS	558	630	552	512	546	2,798
9	BRONCHODILATORS	558	597	546	466	516	2,683
10	THYROID_HORMONES	497	538	503	496	508	2,542
11	ANTIDIABETIC_AGENTS	444	481	396	362	396	2,079
12	ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS	394	459	407	372	373	2,005
13	ANTIHYPERTENSIVE_COMBINATIONS	423	439	401	340	322	1,925
14	OPHTHALMIC_PREPARATIONS	301	345	351	351	388	1,736
15	PROTON_PUMP_INHIBITORS	278	328	274	256	293	1,429
16	ANTICONVULSANTS	241	310	253	243	233	1,280
18	BETA-ADRENERGIC_BLOCKING_AGENTS	307	266	181	181	168	1,103
19	IRON_PRODUCTS	218	211	245	216	123	1,013
20	ANTIHISTAMINES	205	181	141	199	195	921
21	CEPHALOSPORINS	186	173	191	172	149	871
22	NASAL_PREPARATIONS	188	166	215	175	121	865
23	UPPER_RESPIRATORY_COMBINATIONS	177	161	243	114	127	822
24	CALCIUM_CHANNEL_BLOCKING_AGENTS	160	148	147	141	208	804
25	ADRENAL_CORTICAL_STEROIDS	156	158	164	179	124	781
26	ANTIVIRAL_AGENTS	120	140	170	158	152	740
27	ANTIEMETIC/ANTIVERTIGO_AGENTS	131	148	159	149	137	724
28	DIURETICS	151	146	127	147	145	716
29	ANXIOLYTICSEDATIVESAND_HYPNOTICS	125	143	134	131	104	637
30	ANGIOTENSIN_II_INHIBITORS	90	117	114	103	155	579

Table 4.16: Top 30 two-TC1S1 classes polypharmacy ranked by their occurrences

	Two-TC1S1 Classes	Number of Occurrence					Total
		2011	2012	2013	2014	2015	
1	ANALGESICS--PENICILLINS	195	216	245	245	268	1,169
2	ANALGESICS--MUSCLE_RELAXANTS	177	184	188	195	177	921
3	ANALGESICS--MACROLIDE_DERIVATIVES	153	151	137	138	30	609
4	ANTIHYPERLIPIDEMIC_AGENTS-- BETA_ADRENERGIC_BLOCKING_AGENTS	92	113	90	56	51	402
5	ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- ANTIHYPERLIPIDEMIC_AGENTS	85	73	80	72	59	369
6	ANTIHYPERTENSIVE_COMBINATIONS-- ANTIHYPERLIPIDEMIC_AGENTS	80	94	66	50	61	351
7	ANTIDIABETIC_AGENTS-- ANTIHYPERLIPIDEMIC_AGENTS	63	83	68	68	56	338
8	ANALGESICS--DERMATOLOGICAL_AGENTS	57	51	53	55	106	322
9	ADRENAL_CORTICAL_STEROIDS-- BRONCHODILATORS	66	68	71	65	49	319
10	BRONCHODILATORS-- RESPIRATORY_INHALANT_PRODUCTS	73	82	68	45	40	308
11	ANTIDIABETIC_AGENTS-- ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS	66	66	60	57	50	299
12	ANTIHYPERLIPIDEMIC_AGENTS-- ANTIHYPERTENSIVE_COMBINATIONS	56	64	65	54	57	296
13	ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- DIURETICS	58	64	46	57	58	283
14	ANALGESICS--ANTICONVULSANTS	48	61	39	55	78	281
15	ANTIHYPERLIPIDEMIC_AGENTS-- ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS	57	67	69	52	35	280
16	ANALGESICS--SEX_HORMONES	59	60	51	57	51	278
17	ANTIDEPRESSANTS--CNS_STIMULANTS	33	61	43	71	60	268
18	BRONCHODILATORS--LEUKOTRIENE_MODIFIERS	72	59	53	38	41	263
19	ANALGESICS--PROTON_PUMP_INHIBITORS	55	41	46	58	60	260
20	ANTIDEPRESSANTS--SEX_HORMONES	57	54	36	53	52	252
21	SEX_HORMONES--THYROID_HORMONES	48	64	54	39	37	242
22	ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- BETA_ADRENERGIC_BLOCKING_AGENTS	46	49	48	48	40	231
23	ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- CALCIUM_CHANNEL_BLOCKING_AGENTS	41	49	40	48	51	229
24	ANALGESICS--CEPHALOSPORINS	49	41	37	58	38	223
25	ANTIHYPERLIPIDEMIC_AGENTS-- THYROID_HORMONES	33	51	54	36	49	223
26	ANTIDEPRESSANTS--THYROID_HORMONES	51	55	39	32	41	218
27	ANTIHYPERLIPIDEMIC_AGENTS-- PROTON_PUMP_INHIBITORS	49	37	44	36	52	218
28	ANTIADRENERGIC_AGENTSCENTRALLY_ACTING-- CNS_STIMULANTS	44	42	40	51	34	211
29	BRONCHODILATORS--PENICILLINS	44	46	40	40	40	210
30	DERMATOLOGICAL_AGENTS--PENICILLINS	39	40	36	43	47	205

In general, the two-class polypharmacy of TC1S1 have lower occurrences than the TC1 two-classes polypharmacy. This is expected given the much larger number of TC1S1 classes.

Table 4.17: Top 30 three-TC1S1 classes polypharmacy ranked by their occurrences

	Three-TC1S1 Classes	Number of Occurrence					Total
		2011	2012	2013	2014	2015	
1	ANTIDIABETIC_AGENTS-- ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- ANTIHYPERTENSIVE_COMBINATIONS	39	37	39	33	37	185
2	ANTIDIABETIC_AGENTS-- ANTIHYPERTENSIVE_COMBINATIONS-- ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS	25	30	28	35	39	157
3	ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- ANTIHYPERTENSIVE_COMBINATIONS-- BETA_ADRENERGIC_BLOCKING_AGENTS	30	31	16	23	16	116
4	ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- BETA_ADRENERGIC_BLOCKING_AGENTS--DIURETICS	13	16	24	17	16	86
5	ANTIHYPERTENSIVE_COMBINATIONS-- ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- ANTIDIABETIC_AGENTS	13	21	11	21	17	83
6	ANTIHYPERTENSIVE_COMBINATIONS-- BETA_ADRENERGIC_BLOCKING_AGENTS--DIURETICS	16	31	18	7	10	82
7	ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- ANTIHYPERTENSIVE_COMBINATIONS-- ANTIDIABETIC_AGENTS	9	17	10	15	29	80
8	ANTIHYPERTENSIVE_COMBINATIONS-- ANTIHYPERTENSIVE_COMBINATIONS-- BETA_ADRENERGIC_BLOCKING_AGENTS	28	14	15	8	13	78
9	ADRENAL_CORTICAL_STEROIDS-- BRONCHODILATORS--MACROLIDE_DERIVATIVES	17	20	10	19	11	77
10	ANTIHYPERTENSIVE_COMBINATIONS-- BETA_ADRENERGIC_BLOCKING_AGENTS-- CALCIUM_CHANNEL_BLOCKING_AGENTS	18	17	8	15	14	72
11	ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- ANTIHYPERTENSIVE_COMBINATIONS--DIURETICS	13	17	14	14	12	70
12	ANTIHYPERTENSIVE_COMBINATIONS-- ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- BETA_ADRENERGIC_BLOCKING_AGENTS	20	14	10	13	13	70
13	ANALGESICS--ANTICONSULTANTS-- MUSCLE_RELAXANTS	13	10	13	11	19	66
14	ANALGESICS--PENICILLINS-- UPPER_RESPIRATORY_COMBINATIONS	18	11	16	15	6	66
15	BRONCHODILATORS--LEUKOTRIENE_MODIFIERS-- RESPIRATORY_INHALANT_PRODUCTS	19	10	17	13	3	62

4.2.4 Prevalence summary

The highest average number of medication elements in polypharmacy were found in polypharmacy of active ingredients with the range (3.6-3.8), followed by polypharmacy of drugs with the range (3.2-3.4), followed by polypharmacy of TC1S1 with the range (2.8-3.1), and finally the lowest average number of medication elements were found for polypharmacy of TC1 class with the range (2.2-2.4). Overall, averages of the number of medication elements have increased over time (2011-2015), which means an increase in prescriptions trend. Table 4.18 shows summary of the prevalence analysis across all definitions, and Table 4.19 summarizes the proportion of single-element, two-element, and three-element polypharmacy for each definition.

Table 4.18 Summary of prevalence 2011 -2015

	Prevalence of Drug PP	Prevalence of Active ingredients PP	Prevalence of TC1 class PP	Prevalence of TC1S1 class PP
Avg # of PP element	3.365	3.730	2.354	3.002
Avg # of PP	2.035	2.035	2.0352	2.035
Max # elements	34.4	36.6	12.8	23.8
Max # PP per patient	3	3	3	3
#1-element	67854	58,993	79810	71880
#2-element	39481	37840	47672	38910
#3-element	26861	26912	28344	26299

Table 4.19 proportion of single-element, two-element, and three-element of polypharmacy of all definitions.

	Drugs	Active Ingredients	TC1 drug class	TC1S1 drug class
Proportion of single-element	34%	29%	40%	36%
Proportion of two-element	19%	18%	23%	19%
Proportion of three-elements	13%	13%	14%	13%

4.3 Association of polypharmacy with ER

This section provides detailed view of relationship between ER and the number of medication elements (drugs, AIs, or drug classes) in different polypharmacy groups. To summarize these results, it was observed that measure (1) (i.e., The proportion of ER visit to the number of polypharmacy sets in a cluster (i), **ERPP(i)**) that was defined previously in Chapter 3) has been increased with increased number of elements in polypharmacy for all definitions used. This indicates that increasing number of drugs, active ingredients, and drug classes has positive relationship with number of emergency room admissions. It was also noticeable that single active ingredients had the lowest values for this measure followed by single drugs, followed by TC1S1 classes while the highest value were found for single TC1 single classes.

On the other hand, according to the second measure (i.e., **Percentage of ER visits** referred to as **%ER**), it can be observed that the highest proportion of ER visits for a cluster relative to the total of ER visits in the year is found in clusters with 2-4 elements in all categories except for TC1S1 drug class polypharmacy. This may imply that those clusters represent the majority of the polypharmacy detected from patients claims. However, it also reinforces the importance of observing the actual items involved in those polypharmacy. In other words, although using the number of elements as a predictor of problems is one way of looking for polypharmacy impact on ER visits, it is also equally important to investigate and find the patterns of polypharmacy that tend to be associated with ER problems. Supplementary tables of the top 30 single-item, two-item, and three-item polypharmacy categories and their ranking based on ER visits can be found in Appendix A.

Finally, our statistical measures include measuring the probability that a patient who belongs to a certain polypharmacy group would visit the ER. This is referred to as **PPER1(i)** (OR **PPER2(i)** when we assume the conditional independence). These measures show that patients who have higher number of polypharmacy, independent of the basic type, have higher probability to go to the ER than patients with lower polypharmacy elements. It is important to note here that the results for PPER1 and PPER2 were the same and so we included the values for PPER1 in all Tables and Figures in this section.

4.3.1 Relating drug polypharmacy to ER

In this section, we cluster polypharmacy results into groups based on the number of drugs. Then we calculate the three measures we discussed above for each group. **Table 4.20** shows the polypharmacy groups and the three measures (i.e., **ERPP(i)**, **% ER**, and **PPER1(i)**). **Figure 4.1** shows the ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of drugs. **Figure 4.2** shows the proportion of ER visits for given polypharmacy groups based on the number of drugs. **Figure 4.3** shows the probability that a patient in a given polypharmacy group will visit ER in a given year.

Table 4.20: Three measures relating the number of drugs in polypharmacy groups to ER visits

Group	Year	ER	#PP	ERPP = #ER/#PP	Tot ER	#PT	% ER	Tot #PT	ERP	Tot of ERP	PPER
A:1	2011	3076	13737	0.22	24250	10091	0.13	38631	0.30	15.47	0.02
B:2-4	2011	4735	44782	0.11	24250	10395	0.20	38631	0.46	15.47	0.03
C:5-8	2011	5283	67098	0.08	24250	9094	0.22	38631	0.58	15.47	0.04
D:9-12	2011	5503	74485	0.07	24250	8632	0.23	38631	0.64	15.47	0.04
E:>12	2011	5653	77865	0.07	24250	419	0.23	38631	13.49	15.47	0.87
A:1	2012	3282	14431	0.23	12782	10659	0.26	27608	0.31	3.56	0.09
B:2-4	2012	5164	17313	0.30	12782	10977	0.40	27608	0.47	3.56	0.13
C:5-8	2012	2731	6780	0.40	12782	4221	0.21	27608	0.65	3.56	0.18
D:9-12	2012	1033	1939	0.53	12782	1331	0.08	27608	0.78	3.56	0.22
E:>12	2012	572	662	0.86	12782	420	0.04	27608	1.36	3.56	0.38
A:1	2013	12133	38129	0.32	13894	9643	0.23	26590	0.33	3.82	0.09
B:2-4	2013	5266	16029	0.33	13894	10311	0.38	26590	0.51	3.82	0.13
C:5-8	2013	3028	6720	0.45	13894	4243	0.22	26590	0.71	3.82	0.19
D:9-12	2013	1725	2870	0.60	13894	1909	0.12	26590	0.90	3.82	0.24
E:>12	2013	658	720	0.91	13894	484	0.05	26590	1.36	3.82	0.36
A:1	2014	3239	12847	0.25	14349	9598	0.23	26232	0.34	4.29	0.08
B:2-4	2014	5433	16020	0.34	14349	10262	0.38	26232	0.53	4.29	0.12
C:5-8	2014	3267	6958	0.47	14349	4356	0.23	26232	0.75	4.29	0.17
D:9-12	2014	1488	2131	0.70	14349	1460	0.10	26232	1.02	4.29	0.24
E:>12	2014	922	883	1.04	14349	556	0.06	26232	1.66	4.29	0.39
A:1	2015	3030	13321	0.23	14101	9886	0.21	27156	0.31	4.10	0.07
B:2-4	2015	5347	16730	0.32	14101	10644	0.38	27156	0.50	4.10	0.12
C:5-8	2015	3265	7131	0.46	14101	4474	0.23	27156	0.73	4.10	0.18
D:9-12	2015	1542	2295	0.67	14101	1572	0.11	27156	0.98	4.10	0.24
E:>12	2015	917	905	1.01	14101	580	0.07	27156	1.58	4.10	0.39

Figure 4.1 Ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of drugs.

Figure 4.2 Proportion of ER visits for given polypharmacy groups based on the number of drugs.

Figure 4.3 The probability that a patient in a given polypharmacy group will visit ER in a given year.

In general, **ERPP** has been increased with increased number of drugs in all years. This indicates that increasing number of drugs has positive relationship with number of emergency room admissions. It was also noticeable that according to the second measure (i.e., **%ER**), it can be observed that the highest proportion of ER visits for a cluster relative to the total of ER visits in the year is found for clusters with 2-4 drugs for all years. This may imply that those clusters represent the majority of the polypharmacy detected from patients claims.

Finally, we calculate the probability that a patient who belongs to a certain polypharmacy group would visit the ER (i.e., **PPER1 OR PPER2**). These measures show that patients who have higher number of polypharmacy have higher probability to go to the ER than patients with lower polypharmacy elements. In particular, the group with drugs>12 has the highest probability value followed by the group with 9-12 drugs followed by the group with 5-8 followed by the group with 2-4 and finally, the group with single drugs. To sum up, the results of the three measures emphasize that the relationship between number of drugs in polypharmacy and the number of emergency room admissions is positive.

4.3.2 Relating Active Ingredients polypharmacy to ER

In this section, we cluster polypharmacy results into groups based on the number of active ingredients. Then we calculate the three measures we discussed above (in the introduction of section 4.3) for each group. **Table 4.21** shows the polypharmacy groups and the three measures (i.e., **ERPP(i)**, **% ER**, and **PPER1(i)**). **Figure 4.4** shows the ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of active ingredients. **Figure 4.5** shows the proportion of ER visits for given polypharmacy groups based on the number of active

ingredients. **Figure 4.6** shows the probability that a patient in a given polypharmacy group will visit ER in a given year.

Table 4.21: Three measures relating the number of active ingredients in polypharmacy to ER visits

Group	Year	ER	#PP	ERPP = #ER/#PP	Tot ER	#PT	% ER	Tot #PT	ERP	Tot of ERP	PPER
A:1	2011	2577	11964	0.22	11707	8903	0.22	26500	0.29	3.08	0.09
B:2-4	2011	4565	16572	0.28	11707	10759	0.39	26500	0.42	3.08	0.14
C:5-8	2011	2791	7453	0.37	11707	4660	0.24	26500	0.60	3.08	0.19
D:9-12	2011	1020	2183	0.47	11707	1482	0.09	26500	0.69	3.08	0.22
E:>12	2011	754	1033	0.73	11707	696	0.06	26500	1.08	3.08	0.35
A:1	2012	2684	12116	0.22	12144	9048	0.22	26688	0.30	3.17	0.09
B:2-4	2012	4898	16828	0.29	12144	10862	0.40	26688	0.45	3.17	0.14
C:5-8	2012	2758	7214	0.38	12144	4607	0.23	26688	0.60	3.17	0.19
D:9-12	2012	1101	2218	0.50	12144	1536	0.09	26688	0.72	3.17	0.23
E:>12	2012	703	940	0.75	12144	635	0.06	26688	1.11	3.17	0.35
A:1	2013	2908	11798	0.25	14140	9005	0.21	27733	0.32	3.59	0.09
B:2-4	2013	5424	17095	0.32	14140	11245	0.38	27733	0.48	3.59	0.13
C:5-8	2013	3462	7818	0.44	14140	5058	0.24	27733	0.68	3.59	0.19
D:9-12	2013	1365	2312	0.59	14140	1656	0.10	27733	0.82	3.59	0.23
E:>12	2013	981	1107	0.89	14140	769	0.07	27733	1.28	3.59	0.36
A:1	2014	2731	11258	0.24	14349	8496	0.19	26544	0.32	3.94	0.08
B:2-4	2014	5326	16150	0.33	14349	10552	0.37	26544	0.50	3.94	0.13
C:5-8	2014	3468	7716	0.45	14349	4949	0.24	26544	0.70	3.94	0.18
D:9-12	2014	1587	2450	0.65	14349	1714	0.11	26544	0.93	3.94	0.24
E:>12	2014	1237	1265	0.98	14349	833	0.09	26544	1.48	3.94	0.38
A:1	2015	2436	11342	0.21	14101	8503	0.17	27464	0.29	3.83	0.07
B:2-4	2015	5291	17167	0.31	14101	11171	0.38	27464	0.47	3.94	0.12
C:5-8	2015	3521	8028	0.44	14101	5174	0.25	27464	0.68	3.94	0.17
D:9-12	2015	1698	2629	0.65	14101	1826	0.12	27464	0.93	3.94	0.24
E:>12	2015	1155	1216	0.95	14101	790	0.08	27464	1.46	3.94	0.37

Figure 4.4 Ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of active ingredients.

Figure 4.5 Proportion of ER visits for given polypharmacy groups based on the number of active ingredients.

Figure 4.6 The probability that a patient in a given polypharmacy group will visit ER in a given year.

In analysis, **ERPP** has been increased with increased number of active ingredients in all years. This indicates that increasing number of active ingredients and the number of emergency room admissions are positively correlated. We can observe that based on the second measure (i.e., **%ER**), the highest proportion of ER visits for a cluster relative to the total of ER visits in the year is found for clusters with 2-4 active ingredients for all years. This could imply that those clusters represent the biggest group with the highest number of polypharmacy detected from patients claims.

Finally, we calculate the probability that a patient who belongs to a certain polypharmacy group would visit the ER (i.e., **PPER1 OR PPER2**). These measures show that patients who have higher number of polypharmacy have higher probability to go to the ER than patients with lower polypharmacy elements. In particular, the group with active ingredients >12 has the highest probability value followed by the group with 9-12 drugs followed by the group with 5-8 followed by the group with 2-4 and finally, the group with single active ingredients. In conclusion, the results of the three measures emphasize the positive relationship between number of active ingredients in polypharmacy and the number of emergency room admissions.

4.3.3 Relating polypharmacy based on drug-class to ER

In this section, we cluster polypharmacy results into groups based on the number of drug classes. We start by TC1 drug class and then we perform the same calculations for TC1S1 drug class. We calculate the three measures we discussed above (in the introduction of section 4.3) for each polypharmacy cluster. **Table 4.22** shows the polypharmacy groups and the three

measures (i.e., **ERPP(i)**, **% ER**, and **PPER1(i)**) for TC1 drug class. **Figure 4.7** shows the ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of TC1 drug classes. **Figure 4.8** shows the proportion of ER visits for given polypharmacy groups based on the number of TC1 drug classes. **Figure 4.9** shows the probability that a patient in a given polypharmacy group will visit ER in a given year.

Table 4.22: Three measures relating the number of TC1 classes in polypharmacy to ER visits

Group	Year	ER	#PP	ERPP = #ER/#PP	Tot ER	#PT	% ER	Tot #PT	ERP	Tot of ERP	PPER
A:1	2011	3910	16467	0.24	11707	11542	0.33	24724	0.34	2.81	0.12
B:2-4	2011	5783	18661	0.31	11707	10791	0.49	24724	0.54	2.81	0.19
C:5-8	2011	1901	3933	0.48	11707	2288	0.16	24724	0.83	2.81	0.30
D:9-12	2011	113	143	0.79	11707	102	0.01	24724	1.11	2.81	0.39
E:>12	2011	0	1	0.00	11707	1	0.00	24724	0.00	2.81	0.00
A:1	2012	4214	17399	0.24	12782	12264	0.33	25989	0.34	3.24	0.11
B:2-4	2012	6317	19543	0.32	12782	11271	0.49	25989	0.56	3.24	0.17
C:5-8	2012	2101	4024	0.52	12782	2350	0.16	25989	0.89	3.24	0.28
D:9-12	2012	150	154	0.97	12782	104	0.01	25989	1.44	3.24	0.45
E:>12	2012	0	0	-	12782	0	0.00	25989	-	3.24	-
A:1	2013	4391	16408	0.27	14140	11783	0.31	25772	0.37	5.70	0.07
B:2-4	2013	6990	19304	0.36	14140	11288	0.49	25772	0.62	5.70	0.11
C:5-8	2013	2521	4220	0.60	14140	2563	0.18	25772	0.98	5.70	0.17
D:9-12	2013	236	197	1.20	14140	137	0.02	25772	1.72	5.70	0.30
E:>12	2013	2	1	2.00	14140	1	0.00	25772	2.00	5.70	0.35
A:1	2014	4244	15546	0.27	14349	11114	0.30	24679	0.38	4.11	0.09
B:2-4	2014	6933	18584	0.37	14357	10770	0.48	24679	0.64	4.11	0.16
C:5-8	2014	2840	4467	0.64	14357	2628	0.20	24679	1.08	4.11	0.26
D:9-12	2014	332	241	1.38	14357	166	0.02	24679	2	4.11	0.49
E:>12	2014	0	1	0	14357	1	0	24679	0	4.11	0
A:1	2015	3880	15345	0.25	13452	10928	0.30	24440	0.36	3.58	0.10
B:2-4	2015	6403	18708	0.34	13452	10764	0.48	24440	0.59	3.58	0.17
C:5-8	2015	2931	4460	0.66	13452	2588	0.20	24440	1.13	3.58	0.32
D:9-12	2015	238	229	1.04	13452	159	0.02	24440	1.50	3.58	0.42
E:>12	2015	0	1	0.00	13452	1	0.00	24440	0.00	3.58	0.00

Figure 4.7 Ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of TC1 drug class.

Figure 4.8 Proportion of ER visits for given polypharmacy groups based on the number of TC1 drug class.

Figure 4.9 The probability that a patient in a given polypharmacy group will visit ER in a given year.

From Table 4.22 and Figure 4.7 we can observe **ERPP** has been increased with increased number of TC1 drug classes in all years. This indicates that increasing number of TC1 classes has positive relationship with number of emergency room admissions. An exception case was for group E (i.e., which involves polypharmacy with classes greater than 12). This group has very low ratio for **ERPP**. This is explained given that there are much less polypharmacy groups for higher number of elements (i.e., as thresholds for polypharmacy increase, the number of polypharmacy sets found for these thresholds decrease). As a result, no polypharmacy sets were found for thresholds greater than 12 in these years (2011, 2012, 2014, and 2015). However, the remarkable increase for this ratio in 2013 is because this group (E:>12) contains only one patient who has 2 ER visits and one polypharmacy instance with 13 TC1 drug classes. Thus, the ratio $\#ER/\#PP$ value was high ($2/1=2$) for this case.

On the other hand, we can observe that based on the second measure (i.e., **%ER**), the highest proportion of ER visits for a cluster relative to the total of ER visits in the year is found for clusters with 2-4 TC1 drug class for all years. This could imply that those clusters represent the biggest group with the highest number of polypharmacy detected from patients claims. This group is followed by group A: single TC1 drug classes, followed by group C: 5-8, followed by group D:9-12, and finally group E: >12 which has the lowest proportion of ER visits relative to the total ER visits.

Finally, we calculate the probability that a patient who belongs to a certain polypharmacy group would visit the ER (i.e., **PPER1 OR PPER2**). These measures show that patients who have higher number of polypharmacy have higher probability to go to the ER than patients with lower polypharmacy elements. This was true starting from group D: 9-12 to group A: single TC1 drug classes. The group E with higher than 12 classes has very low probability due to the poor number

of polypharmacy in this group. The probability for this group has only increased in 2013 as the #ER visits was 2 and the number of the patients was 1, which makes the ratio $ERP(i) = \frac{\#ER(i)}{\#PT(i)}$ relatively high. To sum up, the results of the three measures emphasize the positive relationship between number of TC1 drug classes in polypharmacy and the number of emergency room admissions. As for TC1S1 drug class, **Table 4.23** shows the polypharmacy groups and the three measures (i.e., **ERPP(i)**, **% ER**, and **PPER1(i)**) for TC1S1 drug class. **Figure 4.10** shows the ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of TC1S1 drug classes. **Figure 4.11** shows the proportion of ER visits for given polypharmacy groups based on the number of TC1S1 drug classes. **Figure 4.12** shows the probability that a patient in a given polypharmacy group will visit ER in a given year.

Table 4.23: Three measures relating the number of TC1S1 classes in polypharmacy to ER visits

Group	Year	ER	#PP	ERPP = #ER/#PP	Tot ER	#PT	% ER	Tot #PT	ERP	Tot of ERP	PPER
A:1	2011	3347	14641	0.23	11707	10565	0.29	25639	0.32	3.51	0.09
B:2-4	2011	5043	16939	0.30	11707	10457	0.43	25639	0.48	3.51	0.14
C:5-8	2011	2329	6048	0.39	11707	3581	0.20	25639	0.65	3.51	0.19
D:9-12	2011	801	1346	0.60	11707	873	0.07	25639	0.92	3.51	0.26
E:>12	2011	187	231	0.81	11707	163	0.02	25639	1.15	3.51	0.33
A:1	2012	3620	15441	0.23	12782	11219	0.28	26982	0.32	3.92	0.08
B:2-4	2012	5424	17767	0.31	12782	10931	0.42	26982	0.50	3.92	0.13
C:5-8	2012	2672	6322	0.42	12782	3777	0.21	26982	0.71	3.92	0.18
D:9-12	2012	818	1336	0.61	12782	886	0.06	26982	0.92	3.92	0.24
E:>12	2012	248	254	0.98	12782	169	0.02	26982	1.47	3.92	0.37
A:1	2013	3732	14451	0.26	14140	10725	0.26	26756	0.35	4.37	0.08
B:2-4	2013	5802	17348	0.33	14140	10826	0.41	26756	0.54	4.37	0.12
C:5-8	2013	3206	6588	0.49	14140	3999	0.23	26756	0.80	4.37	0.18
D:9-12	2013	1073	1450	0.74	14140	1003	0.08	26756	1.07	4.37	0.25
E:>12	2013	327	293	1.12	14140	203	0.02	26756	1.61	4.37	0.37
A:1	2014	3618	13778	0.26	14532	10133	0.25	25760	0.36	4.70	0.08
B:2-4	2014	5667	16497	0.34	14532	10248	0.39	25760	0.55	4.70	0.12
C:5-8	2014	3457	6655	0.52	14532	4012	0.24	25760	0.86	4.70	0.18
D:9-12	2014	1171	1551	0.75	14532	1020	0.08	25760	1.15	4.70	0.24
E:>12	2014	619	550	1.13	14532	347	0.04	25760	1.78	4.70	0.38
A:1	2015	3359	14133	0.24	14101	10355	0.24	26498	0.32	4.53	0.07
B:2-4	2015	5695	17414	0.33	14101	10746	0.40	26498	0.53	4.53	0.12
C:5-8	2015	3347	6802	0.49	14101	4056	0.24	26498	0.83	4.53	0.18
D:9-12	2015	1295	1669	0.78	14101	1099	0.09	26498	1.18	4.53	0.26
E:>12	2015	405	364	1.11	14101	242	0.03	26498	1.67	4.53	0.37

Figure 4.10 Ratio of ER visits to the number of polypharmacy for 5 polypharmacy groups based on the number of TC1S1 drug class.

Figure 4.11 Proportion of ER visits for given polypharmacy groups based on the number of TC1S1 drug class.

Figure 4.12 The probability that a patient in a given polypharmacy group will visit ER in a given year.

In analysis, **ERPP** has been increased with increased number of active ingredients in all years. This indicates that increasing number of TC1S1 drug class elements and the number of emergency room admissions are positively correlated. We can observe that based on the second measure (i.e., **%ER**), the highest proportion of ER visits for a cluster relative to the total of ER visits in the year is found for clusters with 2-4 TC1S1 drug classes for all years. This means that those clusters have highest number of polypharmacy detected from patients claims. After that, we calculate the probability that a patient who belongs to a certain polypharmacy group would visit the ER (i.e., **PPER1 OR PPER2**). These measures show that patients who have higher number of polypharmacy have higher probability to go to the ER than patients with lower polypharmacy elements. Thus, the group with TC1S1 drug classes >12 has the highest probability value followed by the group with 9-12 drugs followed by the group with 5-8 followed by the group with 2-4 and finally, the group with single drug classes of this type. In conclusion, the results of the three measures emphasize the positive relationship between number of TC1S1 drug classes in polypharmacy and the number of ER visits.

Finally, we combine the results for all years for every definition. **Table 4.24** shows a summary of average values for all definitions and for all years.

Table 4.24: Summary of average values for all definitions and for all years.

Type	Group	ER	#PP	ERPP= #ER/ #pp	Tot ER	#PT	% ER	Tot #PT	ERP	Tot of ERP	PPER
drug	A:1	3168.8	13423	0.24	13259.2	8903	0.24	26500	0.36	3.32	0.11
drug	B:2-4	5189	16490.4	0.31	13259.2	10759	0.39	26500	0.48	3.32	0.15
drug	C:5-8	2957	6843.2	0.43	13259.2	4660	0.22	26500	0.63	3.32	0.19
drug	D:9-12	1236	2014.8	0.61	13259.2	1482	0.09	26500	0.83	3.32	0.25
drug	E:>12	708.4	764.8	0.93	13259.2	696	0.05	26500	1.02	3.32	0.31

AI	A:1	2667.2	11695.6	0.23	13288.2	8903	0.20	26500	0.30	3.76	0.08
AI	B:2-4	5100.8	16762.4	0.30	13288.2	10759	0.38	26500	0.47	3.76	0.13
AI	C:5-8	3200	7645.8	0.42	13288.2	4660	0.24	26500	0.69	3.76	0.18
AI	D:9-12	1354.2	2358.4	0.57	13288.2	1482	0.10	26500	0.91	3.76	0.24
AI	E:>12	966	1112.2	0.87	13288.2	696	0.07	26500	1.39	3.76	0.37
TC1	A:1	4127.8	16233	0.25	13286	8903	0.31	26500	0.46	1.74	0.27
TC1	B:2-4	6485.2	18960	0.34	13286	10759	0.49	26500	0.60	1.74	0.35
TC1	C:5-8	2458.8	4220.8	0.58	13286	4660	0.19	26500	0.53	1.74	0.30
TC1	D:9-12	213.8	192.8	1.11	13286	1482	0.02	26500	0.14	1.74	0.08
TC1	E:>12	0.4	0.8	0.50	13286	696	0.00	26500	0.00	1.74	0.00
TC1S1	A:1	3535.2	14488.8	0.24	13452.4	8903	0.26	26500	0.40	2.76	0.14
TC1S1	B:2-4	5526.2	17193	0.32	13452.4	10759	0.41	26500	0.51	2.76	0.19
TC1S1	C:5-8	3002.2	6483	0.46	13452.4	4660	0.22	26500	0.64	2.76	0.23
TC1S1	D:9-12	1031.6	1470.4	0.70	13452.4	1482	0.08	26500	0.70	2.76	0.25
TC1S1	E:>12	357.2	338.4	1.06	13452.4	696	0.03	26500	0.51	2.76	0.19

We can observe from Table 4.24 that single active ingredients had the lowest values for ERPP followed by single drugs, followed by single TC1S1 classes while the highest value were found for single TC1 single classes. This is naturally as drugs with single active ingredients should be associated with less risk and drug classes that contains more elements are more likely to be associated with higher risk.

4.4 Richness and Over-Representation

As discussed in Chapter 3, the richness of a polypharmacy is used to measure the proportion of the actual observation to the expected observation. We study richness using two points of view: richness of occurrence and richness of occurrence with ER. One point to consider here is that richness could not be calculated for combinations of drug/active ingredients/drug classes if the occurrences of their single components could not be found. i.e., richness of **AMOXICILLIN--IBUPROFEN** cannot be calculated if the occurrence of AMOXICILLIN or IBUPROFEN as single elements was not reported.

The next sub-sections contain multiple tables with richness values for the top 30 two-element polypharmacy sets ranked based on ER visits. We will identify an exemplary case where the richness defined for the co-occurrence of two items (i.e., two drugs, two active ingredients, or two drug classes) have noticeable lower values in comparison to the richness of ER. Tables for richness for the top 30 three-element polypharmacy can be found in Appendix B.

4.4.1 Richness of polypharmacy using number of drugs

This section contains tables with richness values for the top 30 two-drug polypharmacy sets ranked based on ER visits. **Table 4.25** shows the top drug-pairs and their co-occurrences

probability ranked by ER total and **Table 4.26** shows the individual and joint probability of occurrence of the top 30 two-drug polypharmacy (sorted by ER total) with richness of occurrence and ER.

Table 4.25: Top 30 drug-pairs and their co-occurrences probability ranked by ER total.

	Two-drug polypharmacy	Occ	ER	#ER/#occ	p(two-occ)**
1	HYDROCO/APAP--IBUPROFEN	176	147	0.84	0.0045
2	AMOXICILLIN--IBUPROFEN	294	94	0.32	0.0074
3	AMOXICILLIN--HYDROCO/APAP	157	64	0.41	0.0040
4	APAP/CODEINE--AZITHROMYCIN	116	56	0.48	0.0029
5	ALBUTEROL--AMOXICILLIN	84	56	0.67	0.0021
6	AMOXICILLIN--AZITHROMYCIN	96	54	0.56	0.0024
7	AZITHROMYCIN--HYDROCO/APAP	83	53	0.64	0.0021
8	CYCLOBENZAPR--HYDROCO/APAP	77	52	0.68	0.0020
9	CYCLOBENZAPR--IBUPROFEN	82	50	0.61	0.0021
10	IBUPROFEN--OXYCOD/APAP	67	47	0.70	0.0017
11	IBUPROFEN--PREDNISONE	14	46	3.29	0.0004
12	AMLODIPINE--LISINOPRIL	143	43	0.30	0.0036
13	AZITHROMYCIN--IBUPROFEN	120	43	0.36	0.0030
14	CLINDAMYCIN--HYDROCO/APAP	41	43	1.05	0.0010
15	AZITHROMYCIN--PREDNISONE	63	36	0.57	0.0016
16	APAP/CODEINE--IBUPROFEN	48	36	0.75	0.0012
17	HYDROCO/APAP-- PROMETHAZINE	23	30	1.30	0.0006
18	LISINOPRIL--SIMVASTATIN	221	29	0.13	0.0056
19	IBUPROFEN--TRAMADOL HCL	26	29	1.12	0.0007
20	ALBUTEROL--PREDNISONE	32	28	0.88	0.0008
21	CYCLOBENZAPR--NAPROXEN	66	27	0.41	0.0017
22	ALBUTEROL--AZITHROMYCIN	59	26	0.44	0.0015
23	HYDROCO/APAP--PENICILLN VK	53	26	0.49	0.0013
24	AMOXICILLIN--PREDNISONE	48	26	0.54	0.0012
25	AMLODIPINE--HYDROCHLOROT	96	23	0.24	0.0024
26	CEPHALEXIN--HYDROCO/APAP	51	23	0.45	0.0013
27	AMOXICILLIN--APAP/CODEINE	63	22	0.35	0.0016
28	SERTRALINE--TRAZODONE	25	21	0.84	0.0006
29	HYDROCO/APAP--NAPROXEN	37	20	0.54	0.0009
30	HYDROCO/APAP--OXYCOD/APAP	25	20	0.80	0.0006

**p(two-occ) here represents the joint probability for the pairs.

Table 4.26: Individual and joint probability of occurrence for the top 30 two-drug polypharmacy (sorted by ER total) with richness of occurrence and ER.

	part1	part2	part1- occ	part2- occ	p(part1- occ)	p(part2- occ)	Occ- richness	part1- ER Occ	part2- ER Occ	p(part1- ERocc)	p(part2- ERocc)	p(two- case- ER)	ER- richness
1	HYDROCO/APAP	IBUPROFEN	1238	1675	0.0182	0.0247	9.90	698	691	0.044	0.043	0.013	6.756
2	AMOXICILLIN	IBUPROFEN	4471	1675	0.0659	0.0247	4.58	1190	691	0.074	0.043	0.008	2.534
3	AMOXICILLIN	HYDROCO/APAP	4471	1238	0.0659	0.0182	3.31	1190	698	0.074	0.044	0.006	1.708
4	APAP/CODEINE	AZITHROMYCIN	614	3180	0.0090	0.0469	6.93	304	891	0.019	0.056	0.005	4.583
5	ALBUTEROL	AMOXICILLIN	785	4471	0.0116	0.0659	2.79	275	1190	0.017	0.074	0.005	3.793
6	AMOXICILLIN	AZITHROMYCIN	4471	3180	0.0659	0.0469	0.79	1190	891	0.074	0.056	0.005	1.129
7	AZITHROMYCIN	HYDROCO/APAP	3180	1238	0.0469	0.0182	2.46	891	698	0.056	0.044	0.005	1.889
8	CYCLOBENZAPR	HYDROCO/APAP	260	1238	0.0038	0.0182	27.90	122	698	0.008	0.044	0.004	13.536
9	CYCLOBENZAPR	IBUPROFEN	260	1675	0.0038	0.0247	21.96	122	691	0.008	0.043	0.004	13.148
10	IBUPROFEN	OXYCOD/APAP	1675	324	0.0247	0.0048	14.40	691	175	0.043	0.011	0.004	8.616
11	IBUPROFEN	PREDNISONE	1675	436	0.0247	0.0064	2.24	691	190	0.043	0.012	0.004	7.767
12	AMLODIPINE	LISINOPRIL	684	1737	0.0101	0.0256	14.04	81	291	0.005	0.018	0.004	40.440
13	AZITHROMYCIN	IBUPROFEN	3180	1675	0.0469	0.0247	2.63	891	691	0.056	0.043	0.004	1.548
14	CLINDAMYCIN	HYDROCO/APAP	260	1238	0.0038	0.0182	14.85	77	698	0.005	0.044	0.004	17.735
15	AZITHROMYCIN	PREDNISONE	3180	436	0.0469	0.0064	5.30	891	190	0.056	0.012	0.003	4.714
16	APAP/CODEINE	IBUPROFEN	614	1675	0.0090	0.0247	5.44	304	691	0.019	0.043	0.003	3.799
17	HYDROCO/APAP	PROMETHAZINE	1238	187	0.0182	0.0028	11.59	698	85	0.044	0.005	0.003	11.209
18	LISINOPRIL	SIMVASTATIN	1737	1014	0.0256	0.0149	14.63	291	106	0.018	0.007	0.003	20.841
19	IBUPROFEN	TRAMADOL HCL	1675	248	0.0247	0.0037	7.30	691	110	0.043	0.007	0.003	8.458
20	ALBUTEROL	PREDNISONE	785	436	0.0116	0.0064	10.90	275	190	0.017	0.012	0.002	11.879
21	CYCLOBENZAPR	NAPROXEN	260	493	0.0038	0.0073	60.05	122	174	0.008	0.011	0.002	28.195
22	ALBUTEROL	AZITHROMYCIN	785	3180	0.0116	0.0469	2.76	275	891	0.017	0.056	0.002	2.352
23	HYDROCO/APAP	PENICILLIN VK	1238	269	0.0182	0.0040	18.56	698	94	0.044	0.006	0.002	8.784
24	AMOXICILLIN	PREDNISONE	4471	436	0.0659	0.0064	2.87	1190	190	0.074	0.012	0.002	2.549
25	AMLODIPINE	HYDROCHLOROT	684	463	0.0101	0.0068	35.35	81	85	0.005	0.005	0.002	74.053
26	CEPHALEXIN	HYDROCO/APAP	538	1238	0.0079	0.0182	8.93	196	698	0.012	0.044	0.002	3.727
27	AMOXICILLIN	APAP/CODEINE	4471	614	0.0659	0.0090	2.68	1190	304	0.074	0.019	0.002	1.348
28	SERTRALINE	TRAZODONE	539	80	0.0079	0.0012	67.61	97	13	0.006	0.001	0.002	369.165
29	HYDROCO/APAP	NAPROXEN	1238	493	0.0182	0.0073	7.07	698	174	0.044	0.011	0.002	3.650
30	HYDROCO/APAP	OXYCOD/APAP	1238	324	0.0182	0.0048	7.27	698	175	0.044	0.011	0.002	3.630

The following explains the table labels for Table 4.26 and subsequent richness tables:

- Part1 and part2 refers to the first element and the second element in the pair, respectively.
- Part1-occ and part2-occ refers to the number of occurrence for element1 and element2, respectively. This represents the times that an element occurs individually in a single round.

- $p(\text{part1-occ})$ and $p(\text{part2-occ})$ refers to the probability that element1 and element2 occurs individually in the dataset, respectively.
- Occ-richness is the richness measure for a pair with respect to the occurrence.
- Part1-ER Occ and part2-ER Occ refers to the number of occurrence with ER for element1 and element2, respectively. This represents the times that an element occurs individually with ER visits in a single round.
- $p(\text{part1-ERocc})$ and $p(\text{part2-ERocc})$ refers to the probability that element1 and element2 occurs individually with ER visits in the dataset, respectively.
- $P(\text{two-case-ER})$ refers to the joint probability that a pair occurs with ER visits.
- ER-richness is the richness measure for a pair with respect to ER visits.

As shown in the Table 4.25 and Table 4.26, the richness of **(HYDROCO/APAP--IBUPROFEN)** is equal to 60.05 and the occurrences of HYDROCO/APAP and IBUPROFEN separately are found as **(CYCLOBENZAPR: 260, NAPROXEN: 493)**. The expected observation for their joint occurrence is defined by the product of their probability, i.e, multiplication of 0.0038 and 0.0073. It can be observed that the actual observation of their co-occurrence is much higher than the expected observation. This means that they were found to occur together more than expected. The high value of richness for this combination reflects this conclusion. Such conclusion can be taken into consideration by health care specialists to consider the popularity of drug combinations with respect to the occurrence of the individual elements occurrences and maybe prioritize studying the impact of the co-occurrence over the single occurrence for some situations.

Observing the richness with respect to occurrence of ER events reveals that the two drugs **(CYCLOBENZAPR** and **HYDROCO/APAP)** separately have a corresponding ER value of 122, and 698 and probability 0.008 and 0.044, respectively. Their expected observation is equal to 0.000352. On the other hand, the probability of their joint observation was found as 0.004. Thus, they tend to occur jointly with ER more than a parted. Again, this emphasizes the importance of monitoring the effect of their joint polypharmacy on ER more than their single polypharmacy. Moreover, it can be observed that while the pair **(CYCLOBENZAPR--HYDROCO/APAP)** had more richness (over-representation) than **(LISINOPRIL--SIMVASTATIN)** in terms of occurrence **(27.90 vs. 14.63)**, when we consider their association with ER visits, **(LISINOPRIL--SIMVASTATIN)** showed a much more richness **(13.536 vs. 20.84)**. This means that, with respect to drug safety risk, the pair **(LISINOPRIL--SIMVASTATIN)** may pose a significantly higher risk, when compared with **(CYCLOBENZAPR--HYDROCO/APAP)**, even though **(CYCLOBENZAPR--HYDROCO/APAP)** were more over-represented with respect to their frequency of occurrence. Figure 4.13 visualizes the drug richness with respect to occurrence and ER.

Figure 4.13 drug pair occurrence richness plotted against drug pair ER occurrence richness in log scale.

It is important in health care disciplines to look for drug associations with ER that may pose high risk. However, it is also equally important to find drugs that seem to be safe as this would help health care experts to classify them from a safety point of view. Thus, we identify three combinations for all polypharmacy definitions that would be interesting to be reviewed by health care people. This includes:

- Elements with high occurrence richness and low ER richness.
- Elements with high occurrence richness and high ER richness.
- Elements with low occurrence richness and high ER richness.

In **Table 4.27** we list some of the drug pairs from the above groups. Based on the results, there were not any drug pairs found for the case (low occurrence richness and high ER richness).

Table 4.27 Examples of drug pairs with high occurrence richness and low ER richness, high occurrence richness and low ER richness, and low occurrence richness and high ER richness.

Groups	Drug pairs	Occ-Richness	ER-richness
high occurrence richness and high ER richness	BD_PEN_NEEDL--HUMALOG_MIX	14,577.15	44,334.96
	BD_PEN_NEEDL--HUMALOG_KWIK	58,308.62	22,167.48

	HYDROCHLOROT 25MG TAB-- METOPROL TAR 100MG TAB	116,617.24	22,167.48
	MUCINEX CHLD--RESPIRATORY AGENTS	58,308.62	22,167.48
high occurrence richness and low ER richness	OXYCODONE_HCL-- SPIRONOLACTONE	29,154.31	0
	CIPROFLOXACIN-- OXYCODONE/APAP	14,577.15	0
	DONEPEZIL_HCL--TERAZOSIN_HCL	58,308.62	0
	PEDIA-LAX--SENNA	58,308.62	0
	AZITHROMYCIN Z-PAK-- CIPROFLOXACIN	29,154.31	0
	ACCU-CHEK--SOFTCLIX	20,281.25	0
	ALBUTEROL_HFA--ASMANEX_30	29,154.31	0
	AMITRIPTYLINE--TUSSIN_DM	116,617.24	0
	AMMONIUM LACTATE--SOFTCLIX	116,617.24	0
	ASCORBIC ACID TAB 500 MG-- INTEGRA	23,323.44	0
low occurrence richness and high ER richness	-	-	-

4.4.2 Richness of Active Ingredients polypharmacy

This section contains tables with richness values for the top 30 two-active ingredient polypharmacy sets ranked based on ER visits. **Table 4.28** shows the top active ingredient-pairs and their co-occurrences probability ranked by ER total and **Table 4.29** shows the individual and joint probability of occurrence of the top 30 two-active ingredient polypharmacy (sorted by ER total) with richness of occurrence and ER.

Table 4.28: Top 30 active ingredient-pairs and their co-occurrences probability ranked by ER total.

	Two-active ingredient polypharmacy	Occ	ER	#ER/#occ	p(two-occ)
1	ACETAMINOPHEN--HYDROCODONE BITARTRATE	1119	628	0.561	0.0296
2	ACETAMINOPHEN--CODEINE PHOSPHATE	632	317	0.502	0.0167
3	AMOXICILLIN--CLAVULANATE POTASSIUM	678	253	0.373	0.0179
4	ACETAMINOPHEN--OXYCODONE HYDROCHLORIDE	440	235	0.534	0.0116
5	SULFAMETHOXAZOLE--TRIMETHOPRIM	508	189	0.372	0.0134
6	AMOXICILLIN--IBUPROFEN	301	98	0.326	0.0080
7	HYDROCHLOROTHIAZIDE--LISINOPRIL	735	92	0.125	0.0194
8	ALBUTEROL SULFATE--PREDNISONE	75	67	0.893	0.0020
9	AMOXICILLIN--ALBUTEROL SULFATE	103	60	0.583	0.0027
10	ALBUTEROL SULFATE--FLUTICASONE PROPIONATE	190	56	0.295	0.0050
11	CYCLOBENZAPRINE HYDROCHLORIDE--IBUPROFEN	98	56	0.571	0.0026
12	AZITHROMYCIN DIHYDRATE--IBUPROFEN	122	47	0.385	0.0032
13	IBUPROFEN--PREDNISONE	14	46	3.286	0.0004
14	AMLODIPINE BESYLATE--LISINOPRIL	147	43	0.293	0.0039
15	AZITHROMYCIN DIHYDRATE--PREDNISONE	63	36	0.571	0.0017
16	ETHINYL ESTRADIOL--NORETHINDRONE ACETATE	311	36	0.116	0.0082
17	ALBUTEROL SULFATE--BUDESONIDE	100	33	0.330	0.0026
18	CYCLOBENZAPRINE HYDROCHLORIDE--NAPROXEN	74	33	0.446	0.002
19	IBUPROFEN--TRAMADOL HYDROCHLORIDE	31	33	1.065	0.0008
20	AMOXICILLIN--AZITHROMYCIN DIHYDRATE	63	32	0.508	0.0017
21	SERTRALINE HYDROCHLORIDE--TRAZODONE HYDROCHLORIDE	30	31	1.033	0.0008
22	HYDROCODONE BITARTRATE--HOMATROPINE METHYLBROMIDE	94	30	0.319	0.0025
23	ALBUTEROL SULFATE--MONTELUKAST SODIUM	138	29	0.210	0.0036
24	ALBUTEROL SULFATE--PREDNISOLONE	52	29	0.558	0.0014
25	ATENOLOL--CHLORTHALIDONE	145	29	0.200	0.0038
26	LISINOPRIL--SIMVASTATIN	222	29	0.131	0.0059

27	ALBUTEROL SULFATE-- BECLOMETHASONE DIPROPIONATE	104	28	0.269	0.0027
28	ETONOGESTREL--ETHINYL ESTRADIOL	248	28	0.113	0.0066
29	AMLODIPINE BESYLATE-- HYDROCHLOROTHIAZIDE	113	26	0.230	0.003
30	AMOXICILLIN--PREDNISONE	49	26	0.531	0.0013

Table 4.29: Individual and joint probability of occurrence for the top 30 two-active ingredient polypharmacy (sorted by ER total) with richness of occurrence and ER.

	part1	part2	part1- occ	part2- occ	p(part1- occ)	p(part2- occ)	Occ- richness	part1- ER Occ	part2- ER Occ	p(part1- ERocc)	p(part2- ERocc)	p(two- case- ER)	ER- richness
1	ACETAMINOPHEN	HYDROCODONE BITARTRATE	308	47	0.0052	0.0008	7109.37	136	13	0.010	0.001	0.060	6133.93
2	ACETAMINOPHEN	CODEINE PHOSPHATE	308	0	0.0052	0.0000	0.00	136	0	0.010	0.000	0.030	0.00
3	AMOXICILLIN	CLAVULANATE POTASSIUM	4505	0	0.0764	0.0000	0.00	1197	0	0.089	0.000	0.024	0.00
4	ACETAMINOPHEN	OXYCODONE HYDROCHLORIDE	308	255	0.0052	0.0043	515.24	136	140	0.010	0.010	0.022	213.14
5	SULFAMETHOXAZOLE	TRIMETHOPRIM	0	15	0.0000	0.0003	0.00	0	9	0.000	0.001	0.018	0.00
6	AMOXICILLIN	IBUPROFEN	4505	1696	0.0764	0.0287	3.62	1197	696	0.089	0.052	0.009	2.03
7	HYDROCHLOROTHIAZIDE	LISINOPRIL	527	1737	0.0089	0.0294	73.85	100	291	0.007	0.022	0.009	54.60
8	ALBUTEROL SULFATE	PREDNISONE	1875	438	0.0318	0.0074	8.40	556	191	0.041	0.014	0.006	10.90
9	AMOXICILLIN	ALBUTEROL SULFATE	4505	1875	0.0764	0.0318	1.12	1197	556	0.089	0.041	0.006	1.56
10	ALBUTEROL SULFATE	FLUTICASONE PROPIONATE	1875	627	0.0318	0.0106	14.86	556	86	0.041	0.006	0.005	20.22
11	CYCLOBENZAPRINE HYDROCHLORIDE	IBUPROFEN	270	1696	0.0046	0.0287	19.68	125	696	0.009	0.052	0.005	11.12
12	AZITHROMYCIN DIHYDRATE	IBUPROFEN	3233	1696	0.0548	0.0287	2.05	909	696	0.067	0.052	0.004	1.28
13	IBUPROFEN	PREDNISONE	1696	438	0.0287	0.0074	1.73	696	191	0.052	0.014	0.004	5.98
14	AMLODIPINE BESYLATE	LISINOPRIL	722	1737	0.0122	0.0294	10.78	91	291	0.007	0.022	0.004	28.04
15	AZITHROMYCIN DIHYDRATE	PREDNISONE	3233	438	0.0548	0.0074	4.09	909	191	0.067	0.014	0.003	3.58
16	ETHINYL ESTRADIOL	NORETHINDRONE ACETATE	0	10	0.0000	0.0002	0.00	0	1	0.000	0.000	0.003	0.00
17	ALBUTEROL SULFATE	BUDESONIDE	1875	64	0.0318	0.0011	76.64	556	11	0.041	0.001	0.003	93.18
18	CYCLOBENZAPRINE HYDROCHLORIDE	NAPROXEN	270	499	0.004577	0.0085	50.51	125	175	0.009	0.013	0.003	26.05
19	IBUPROFEN	TRAMADOL HYDROCHLORIDE	1696	293	0.028749	0.0050	5.74	696	123	0.052	0.009	0.003	6.66
20	AMOXICILLIN	AZITHROMYCIN DIHYDRATE	4505	3233	0.076365	0.0548	0.40	1197	909	0.089	0.067	0.003	0.51
21	SERTRALINE HYDROCHLORIDE	TRAZODONE HYDROCHLORIDE	603	80	0.010222	0.0014	57.20	106	13	0.008	0.001	0.003	388.48
22	HYDROCODONE BITARTRATE	HOMATROPINE METHYLBROMIDE	47	0	0.000797	0.0000	0.00	13	0	0.001	0.000	0.003	0.00

23	ALBUTEROL SULFATE	MONTELUKAST SODIUM	1875	452	0.031783	0.0077	14.98	556	95	0.041	0.007	0.003	9.48
24	ALBUTEROL SULFATE	PREDNISOLONE	1875	151	0.031783	0.0026	16.89	556	54	0.041	0.004	0.003	16.68
25	ATENOLOL	CHLORTHALIDONE	447	22	0.007577	0.0004	1356.09	66	5	0.005	0.000	0.003	1517.56
26	LISINAPRIL	SIMVASTATIN	1737	1022	0.029444	0.0173	11.50	291	107	0.022	0.008	0.003	16.08
27	ALBUTEROL SULFATE	BECLOMETHASONE DIPROPIONATE	1875	62	0.031783	0.0011	82.28	556	17	0.041	0.001	0.003	51.16
28	ETONOGESTREL	ETHINYL ESTRADIOL	1	0	1.7E-05	0.0000	0.00	0	0	0.000	0.000	0.003	0.00
29	AMLODIPINE BESYLATE	HYDROCHLOROTHIAZIDE	722	527	0.012239	0.0089	27.31	91	100	0.007	0.007	0.002	49.34
30	AMOXICILLIN	PREDNISONE	4505	438	0.076365	0.0074	2.28	1197	191	0.089	0.014	0.002	1.96

The values (0) indicates that those active ingredients were not found within single occurrences of ingredients, for those the value of richness cannot be determined. A noticeable finding here is that although the pair (**BETAMETHASONE DIPROPIONATE--CLOTRIMAZOLE**) has much lower richness value with respect to occurrence when it is compared to its occurrence with ER (**1820.25 vs. 2437.94**). This implies that pair tend to be associated with high risk when it occurs.

In some cases, the richness measure provides additional insight about the safety of two ingredients than the ranking based on ER visits (provided previously in section 4.2). As we discussed earlier, drug polypharmacy may not highlight the problems resulting from single drugs. For this case the active ingredients approach to defining polypharmacy could be more informative and provide a more detailed view of looking at substances and their associations with health problems. **Table 4.30** show few examples of single drugs along with their original ranking based on ER visits for patients, the equivalent active ingredients along with their original ranking based on the ER visits, and finally, the richness measure for these ingredients. It can be observed that even though (**CIPROFLOXACIN HYDROCHLORIDE--DEXAMETHASONE**), (**HYDROCHLOROTHIAZIDE --LOSARTAN POTASSIUM**), and (**ATENOLOL--CHLORTHALIDONE**) ingredients are ranked relatively low based on ER visits sort, they have relatively high richness. This indicates that they jointly tend to have more association with ER than what is expected from the occurrence of individual ingredients. This observation can only be derived by the richness measure.

Table 4.30 Comparison of some single drugs and their continent active ingredients ranking based on ER visits along with the richness of the active ingredient pairs.

Single drug	Multiple AI	ER-Richness
JANUMET ranked 929 by ER.	SITAGLIPTIN PHOSPHATE--METFORMIN HYDROCHLORIDE (ranked 554 by ER)	47.18
COMBIGAN ranked 686 by ER.	BRIMONIDINE TARTRATE--TIMOLOL MALEATE (ranked 563 by ER)	-
DYMISTA ranked 1052 by ER.	AZELASTINEHYDROCHLORIDE--FLUTICASONE PROPIONATE (ranked 907 by ER)	80.31

CIPRODEX ranked 168 by ER.	CIPROFLOXACIN HYDROCHLORIDE-- DEXAMETHASONE (ranked 57 by ER)	259.03
HYZAAR ranked 2078 by ER.	HYDROCHLOROTHIAZIDE--LOSARTAN POTASSIUM (ranked 40 by ER)	86.34
ATENOLOL/CHLORTHALIDONE ranked 1389 by ER.	ATENOLOL--CHLORTHALIDONE (ranked 27 by ER)	1517.55

We use the same groups we identified above in Section 4.4.1 to get some of the combinations that would be interesting to be reviewed by health care people. Again, this includes:

- Elements with high occurrence richness and low ER richness.
- Elements with high occurrence richness and high ER richness.
- Elements with low occurrence richness and high ER richness.

In **Table 4.31** we list some of the active ingredient pairs from the above groups. Based on the richness results, only one active ingredient pair found for the case (low occurrence richness and high ER richness).

Table 4.31 Examples of active ingredient pairs with high occurrence richness and low ER richness, high occurrence richness and low ER richness, and low occurrence richness and high ER richness.

Groups	Active ingredient pairs	Occ-Richness	ER-richness
high occurrence richness and high ER richness	ACETAMINOPHEN-- HYDROCODONE BITARTRATE	7,109.37	6,133.92
	FLUTICASONE PROPIONATE-- SALMETEROL XINAFOATE	32,123.76	2,309.19
	BISOPROLOL FUMARATE-- HYDROCHLOROTHIAZIDE	3,730.31	1,381.50
	DEXAMETHASONE--TOBRAMYCIN	2,556.25	1,569.88
	HYDROCORTISONE ACETATE-- PRAMOXINE HYDROCHLORIDE	36,131.37	60,440.69
	DEXTROMETHORPHAN HYDROBROMIDE--GUAIFENESIN	12,358.57	3,139.77
	CALCIUM ACETATE--SEVELAMER CARBONATE	137,956.15	1,439.06

	ZIPRASIDONE MESYLATE-- ZIPRASIDONE HYDROCHLORIDE	4,379.56	25,903.15
	39328005750--642007630	7,074.67	5,756.25
	193654621--193709021	4,598.53	2,466.96
high occurrence richness and low ER richness	193709021--8290328466	9,197.07	0
	MAGNESIUM HYDROXIDE--SENNA LEAF	45,985.38	0
	49614043612--ZAFIRLUKAST	10,218.97	0
	ADAPALENE--BENZOYL PEROXIDE	12,411.28	0
	DOCUSATE SODIUM--SENNOSIDES	15,328.46	0
	DORZOLAMIDE HYDROCHLORIDE-- TIMOLOL MALEATE	34,489.03	0
	50924098850--50924097110	61,313.84	0
	182101701--MODAFINIL	10,218.97	0
	677007010--99073070805	9,197.07	0
	38142300000--54838014530	18,394.15	0
low occurrence richness and high ER richness	GEMFIBROZIL--LOVASTATIN	9.88933	2,072.25

We plot the trend of active ingredients richness with respect to occurrence and ER in **Figure 4.14**.

Figure 4.14 Relationship between active ingredients occurrence and ER richness using a log scale (logarithms are in base 10).

4.4.3 Richness of drug classes polypharmacy

This section contains tables with richness values for the top 30 two-TC1 drug class polypharmacy sets ranked based on ER visits. **Table 4.32** shows the top TC1 class -pairs and their co-occurrences probability ranked by ER total and **Table 4.33** shows the individual and joint probability of occurrence of the top 30 two-TC1 class polypharmacy (sorted by ER total) with richness of occurrence and ER.

Table 4.32: Top 30 TC1 class-pairs and their co-occurrences probability ranked by ER total.

	TC1 class pairs	occ-Total	ER-Total	#ER/ #occ	p(two- occ)
1	Anti_infectives--Central nervous system agents	3,762	1,856	0.49	0.08
2	Cardiovascular agents-- Metabolic agents	8,224	1,496	0.18	0.17
3	Central nervous system agents--Psychotherapeutic agents	3,072	1,160	0.38	0.06
4	Central nervous system agents--Cardiovascular agents	1,663	686	0.41	0.03
5	Anti_infectives--Respiratory agents	1,893	673	0.36	0.04
6	Central nervous system agents--Hormones/hormone modifiers	1,461	570	0.39	0.03
7	Central nervous system agents--Gastrointestinal agents	1,091	544	0.50	0.02
8	Central nervous system agents--Respiratory agents	1,275	541	0.42	0.03
9	Anti_infectives--Topical agents	1,800	479	0.27	0.04
10	Cardiovascular agents--Central nervous system agents	1,380	447	0.32	0.03

11	Central nervous system agents--Topical agents	1,111	409	0.37	0.02
12	Central nervous system agents-- Metabolic agents	1,196	362	0.30	0.03
13	Hormones/hormone modifiers--Respiratory agents	835	326	0.39	0.02
14	Respiratory agents--Topical agents	1,197	317	0.26	0.03
15	Anti_infectives--Hormones/hormone modifiers	1,075	316	0.29	0.02
16	Central nervous system agents--Nutritional products	602	303	0.50	0.01
17	Cardiovascular agents--Gastrointestinal agents	830	236	0.28	0.02
18	Anti_infectives--Cardiovascular agents	736	221	0.30	0.02
19	Cardiovascular agents--Hormones/hormone modifiers	1,335	214	0.16	0.03
20	Cardiovascular agents--Psychotherapeutic agents	752	185	0.25	0.02
21	Cardiovascular agents--Nutritional products	501	179	0.36	0.01
22	Cardiovascular agents--Topical agents	651	167	0.26	0.01
23	Hormones/hormone modifiers--Topical agents	631	138	0.22	0.01
24	Cardiovascular agents--Respiratory agents	504	131	0.26	0.01
25	Anti_infectives-- Metabolic agents	347	117	0.34	0.01
26	Anti_infectives--Nutritional products	277	114	0.41	0.01
27	Anti_infectives--Gastrointestinal agents	322	112	0.35	0.01
28	Hormones/hormone modifiers--Psychotherapeutic agents	577	108	0.19	0.01
29	Hormones/hormone modifiers--Nutritional products	184	97	1	0.004
30	Gastrointestinal agents--Nutritional products	144	95	1	0.003

Table 4.33: Individual and joint probability of occurrence for the top 30 two-TC1 class polypharmacy (sorted by ER total) with richness of occurrence and ER.

	TC1 class pairs	part1- occ	p(part1- occ)	part2- occ	p(part2- occ)	occ- richness	part1- ERocc	p(part1- ERocc)	part2- ERocc	p(part2- ERocc)	p(two- case- ER)	ER- richness
1	Anti_infectives-- Central nervous system agents	13495	0.17	17160	0.22	2.17	4053	0.1878	6792	0.3147	0.1247	2.11
2	Cardiovascular agents-- Metabolic agents	10883	0.14	5914	0.07	17.07	2245	0.1040	1049	0.0486	0.1005	19.89
3	Central nervous system agents-- Psychotherapeutic agents	17160	0.22	3379	0.04	7.08	6792	0.3147	831	0.0385	0.0780	6.44

4	Central nervous system agents-- Cardiovascular agents	17160	0.22	10883	0.14	1.19	6792	0.3147	2245	0.1040	0.0461	1.41
5	Anti_infectives-- Respiratory agents	13495	0.17	6407	0.08	2.93	4053	0.1878	1647	0.0763	0.0452	3.16
6	Central nervous system agents-- Hormones/hormone modifiers	17160	0.22	8787	0.11	1.29	6792	0.3147	1491	0.0691	0.0383	1.76
7	Central nervous system agents-- Gastrointestinal agents	17160	0.22	2561	0.03	3.32	6792	0.3147	714	0.0331	0.0366	3.51
8	Central nervous system agents-- Respiratory agents	17160	0.22	6407	0.08	1.55	6792	0.3147	1647	0.0763	0.0364	1.51
9	Anti_infectives-- Topical agents	13495	0.17	6588	0.08	2.71	4053	0.1878	1492	0.0691	0.0322	2.48
10	Cardiovascular agents--Central nervous system agents	10883	0.14	17160	0.22	0.99	2245	0.1040	6792	0.3147	0.0300	0.92
11	Central nervous system agents-- Topical agents	17160	0.22	6588	0.08	1.31	6792	0.3147	1492	0.0691	0.0275	1.26
12	Central nervous system agents-- Metabolic agents	17160	0.22	5914	0.07	1.57	6792	0.3147	1049	0.0486	0.0243	1.59
13	Hormones/hormone modifiers-- Respiratory agents	8787	0.11	6407	0.08	1.98	1491	0.0691	1647	0.0763	0.0219	4.16

14	Respiratory agents-- Topical agents	6407	0.08	6588	0.08	3.79	1647	0.0763	1492	0.0691	0.0213	4.04
15	Anti_infectives-- Hormones/hormone modifiers	13495	0.17	8787	0.11	1.21	4053	0.1878	1491	0.0691	0.0212	1.64
16	Central nervous system agents-- Nutritional products	17160	0.22	2258	0.03	2.08	6792	0.3147	669	0.0310	0.0204	2.09
17	Cardiovascular agents-- Gastrointestinal agents	10883	0.14	2561	0.03	3.98	2245	0.1040	714	0.0331	0.0159	4.61
18	Anti_infectives-- Cardiovascular agents	13495	0.17	10883	0.14	0.67	4053	0.1878	2245	0.1040	0.0149	0.76
19	Cardiovascular agents-- Hormones/hormone modifiers	10883	0.14	8787	0.11	1.87	2245	0.1040	1491	0.0691	0.0144	2.00
20	Cardiovascular agents-- Psychotherapeutic agents	10883	0.14	3379	0.04	2.73	2245	0.1040	831	0.0385	0.0124	3.10
21	Cardiovascular agents--Nutritional products	10883	0.14	2258	0.03	2.72	2245	0.1040	669	0.0310	0.0120	3.73
22	Cardiovascular agents--Topical agents	10883	0.14	6588	0.08	1.21	2245	0.1040	1492	0.0691	0.0112	1.56
23	Hormones/hormone modifiers--Topical agents	8787	0.11	6588	0.08	1.46	1491	0.0691	1492	0.0691	0.0093	1.94

24	Cardiovascular agents--Respiratory agents	10883	0.14	6407	0.08	0.97	2245	0.1040	1647	0.0763	0.0088	1.11
25	Anti_infectives--Metabolic agents	13495	0.17	5914	0.07	0.58	4053	0.1878	1049	0.0486	0.0079	0.86
26	Anti_infectives--Nutritional products	13495	0.17	2258	0.03	1.21	4053	0.1878	669	0.0310	0.0077	1.32
27	Anti_infectives--Gastrointestinal agents	13495	0.17	2561	0.03	1.24	4053	0.1878	714	0.0331	0.0075	1.21
28	Hormones/hormone modifiers--Psychotherapeutic agents	8787	0.11	3379	0.04	2.60	1491	0.0691	831	0.0385	0.0073	2.73
29	Hormones/hormone modifiers--Nutritional products	8787	0.11	2258	0.03	1.24	1491	0.0691	669	0.0310	0.0065	3.04
30	Gastrointestinal agents--Nutritional products	2561	0.03	2258	0.03	3.33	714	0.0331	669	0.0310	0.0064	6.23

Cardiovascular agents—Metabolic agents has lower tendency to occur together compared to their tendency to occur together with ER (**17.07 vs. 19.89**). This again could indicate that this pair tend to be associated with higher risk when it occurs. **Figure 4.15** graphs the richness of occurrence and the richness of ER visits values for TC1 drug class pairs.

Figure 4.15 relationship between TC1 class pairs occurrence and ER richness. Logarithms are in base 10.

We now identify the same groups we chose for drug pairs and active ingredient pairs to get some of the TC1 drug class combinations that would be interesting to be reviewed by health care people. Again, this includes:

- Elements with high occurrence richness and low ER richness.
- Elements with high occurrence richness and high ER richness.
- Elements with low occurrence richness and high ER richness.

In **Table 4.34** we list some of the TC1 class pairs from the above groups. Based on the richness results, only one TC1 class pair found for the case (low occurrence richness and high ER richness).

Table 4.34 Example of TC1 class pairs with high occurrence richness and low ER richness, high occurrence richness and low ER richness, and low occurrence richness and high ER richness.

	TC1 class pairs	ER-Richness	Occ-Richness
high occurrence richness and high ER richness	Cardiovascular agents--Metabolic agents	19.88	17.07
	Miscellaneous agents--Psychotherapeutic agents	9.68	17.25
	Nutritional products--Psychotherapeutic agents	0.84	1.33

high occurrence richness and low ER richness	Antineoplastics--Gastrointestinal agents	0.79	1.90
	Cardiovascular agents--Immunologic agents	0.60	1.88
	Alternative medicines--Psychotherapeutic agents	0	2.08
	Antineoplastics--Coagulation modifiers	0	6.19
	Antineoplastics-- Genitourinary tract agents	0	1.49
	Biologicals--Central nervous system agents	0	1.94
	Coagulation modifiers--Genitourinary tract agents	0	2.33
	Genitourinary tract agents--Immunologic agents	0	5.67
low occurrence richness and High ER richness	Gastrointestinal agents--Genitourinary tract agents	8.12	0.30

Table 4.35 summarizes the occurrence richness and the ER richness. We can observe from table 4.36 that the occurrence richness and the ER richness have very similar values for the case of TC1 class definition. This follows our previous discussion in Section 4.2.3 (prevalence of drug class polypharmacy) that defining polypharmacy using TC1 class is not accurate enough in terms of associations with health problems compared to defining polypharmacy using TC1S1 drug class, Active ingredients, OR drugs.

Table 4.35: Summary of Top 30 TC1 class pairs and their richness with respect to occurrence and ER.

TC1 class pairs	Richness-occ	Richness-ERocc
Anti_infectives--Central nervous system agents	2.17	2.11
Cardiovascular agents-- Metabolic agents	17.07	19.89
Central nervous system agents--Psychotherapeutic agents	7.08	6.44
Central nervous system agents--Cardiovascular agents	1.19	1.41
Anti_infectives--Respiratory agents	2.93	3.16
Central nervous system agents--Hormones/hormone modifiers	1.29	1.76

Central nervous system agents--Gastrointestinal agents	3.32	3.51
Central nervous system agents--Respiratory agents	1.55	1.51
Anti_infectives--Topical agents	2.71	2.48
Cardiovascular agents--Central nervous system agents	0.99	0.92
Central nervous system agents--Topical agents	1.31	1.26
Central nervous system agents-- Metabolic agents	1.57	1.59
Hormones/hormone modifiers--Respiratory agents	1.98	4.16
Respiratory agents--Topical agents	3.79	4.04
Anti_infectives--Hormones/hormone modifiers	1.21	1.64
Central nervous system agents--Nutritional products	2.08	2.09
Cardiovascular agents--Gastrointestinal agents	3.98	4.61
Anti_infectives--Cardiovascular agents	0.67	0.76
Cardiovascular agents--Hormones/hormone modifiers	1.87	2.00
Cardiovascular agents--Psychotherapeutic agents	2.73	3.10
Cardiovascular agents--Nutritional products	2.72	3.73
Cardiovascular agents--Topical agents	1.21	1.56
Hormones/hormone modifiers--Topical agents	1.46	1.94
Cardiovascular agents--Respiratory agents	0.97	1.11
Anti_infectives-- Metabolic agents	0.58	0.86
Anti_infectives--Nutritional products	1.21	1.32
Anti_infectives--Gastrointestinal agents	1.24	1.21
Hormones/hormone modifiers--Psychotherapeutic agents	2.60	2.73
Hormones/hormone modifiers--Nutritional products	1.24	3.04
Gastrointestinal agents--Nutritional products	3.33	6.23

Finally, we apply the same richness analysis for TC1S1 class pairs. **Table 4.36** shows the top TC1S1 class -pairs and their co-occurrences probability ranked by ER total and **Table 4.37** shows the individual and joint probability of occurrence for the top 30 two-TC1S1 class polypharmacy (sorted by ER total) with richness of occurrence and ER.

Table 4.36: Top 30 TC1S1 class-pairs and their co-occurrences probability ranked by ER total.

	TC1S1 class pairs	#occ	#ER	#ER/#Occ	P(two-occ)
1	ANALGESICS--MUSCLE_RELAXANTS	921	525	0.57	0.0225
2	ANALGESICS--PENICILLINS	1,169	519	0.44	0.0285
3	ANALGESICS--MACROLIDE_DERIVATIVES	609	335	0.55	0.0149
4	ANALGESICS-- ANTIEMETIC/ANTIVERTIGO_AGENTS	176	208	1.18	0.0043
5	ADRENAL_CORTICAL_STEROIDS-- BRONCHODILATORS	319	192	0.60	0.0078
6	ANALGESICS--ANTICONVULSANTS	281	162	0.58	0.0069
7	ANALGESICS--DERMATOLOGICAL_AGENTS	322	160	0.50	0.0079
8	ANALGESICS--CEPHALOSPORINS	223	123	0.55	0.0054
9	ANALGESICS--PROTON_PUMP_INHIBITORS	260	114	0.44	0.0063
10	ANALGESICS--IRON_PRODUCTS	157	107	0.68	0.0038
11	ANALGESICS--MISCELLANEOUS_ANTIBIOTICS	114	102	0.89	0.0028
12	ANALGESICS--SEX_HORMONES	278	101	0.36	0.0068
13	BRONCHODILATORS--PENICILLINS	210	100	0.48	0.0051
14	BRONCHODILATORS-- RESPIRATORY_INHALANT_PRODUCTS	308	93	0.30	0.0075
15	ANALGESICS--BRONCHODILATORS	149	90	0.60	0.0036
16	ANTIEMETIC/ANTIVERTIGO_AGENTS-- ANALGESICS	89	88	0.99	0.0022
17	ANALGESICS--ANTIDEPRESSANTS	200	88	0.44	0.0049
18	ANALGESICS--QUINOLONES	96	82	0.85	0.0023
19	MACROLIDE_DERIVATIVES--PENICILLINS	148	80	0.54	0.0036
20	ADRENAL_CORTICAL_STEROIDS--ANALGESICS	80	79	0.99	0.0020

21	ANTIDEPRESSANTS--ANTICONVULSANTS	192	76	0.40	0.0047
22	ANALGESICS--LINCOMYCIN_DERIVATIVES	100	75	0.75	0.0024
23	ANTICONVULSANTS--ANALGESICS	165	73	0.44	0.0040
24	ANALGESICS--LAXATIVES	142	70	0.49	0.0035
25	ANALGESICS-- ANTIHYPERTENSIVE_COMBINATIONS	120	67	0.56	0.0029
26	ANALGESICS--DIURETICS	101	66	0.65	0.0025
27	ANALGESICS-- BETA_ADRENERGIC_BLOCKING_AGENTS	138	65	0.47	0.0034
28	BRONCHODILATORS-- LEUKOTRIENE_MODIFIERS	263	62	0.24	0.0064
29	BRONCHODILATORS-- MACROLIDE_DERIVATIVES	175	62	0.35	0.0043
30	ANALGESICS--ADRENAL_CORTICAL_STEROIDS	99	62	0.63	0.0024

Table 4.37: Individual and joint probability of occurrence for the top 30 two-TC1S1 class polypharmacy (sorted by ER total) with richness of occurrence and ER.

	TC1S1 class pairs	part1- occ	p(part 1-occ)	part2- occ	p(part2 -occ)	Occ-R *	part1- ERocc	p(part1- ERocc)	part2- ERocc	p(part2- ERocc)	p(two- case- ER)	ER-R **
1	ANALGESICS-- MUSCLE_RELAXANTS	8519	0.12	441	0.01	30.89	3973	0.2270	166	0.0095	0.0426	19.7
2	ANALGESICS--PENICILLINS	8519	0.12	5593	0.08	3.09	3973	0.2270	1591	0.0909	0.0421	2.04
3	ANALGESICS-- MACROLIDE_DERIVATIVES	8519	0.12	3357	0.05	2.68	3973	0.2270	932	0.0532	0.0272	2.25
4	ANALGESICS-- ANTIEMETIC/ANTIVERTIGO_AGENTS	8519	0.12	724	0.01	3.60	3973	0.2270	420	0.0240	0.0169	3.10
5	ADRENAL_CORTICAL_STEROIDS-- BRONCHODILATORS	781	0.01	2683	0.04	19.18	302	0.0173	723	0.0413	0.0156	21.8
6	ANALGESICS-- ANTICONVULSANTS	8519	0.12	1280	0.02	3.25	3973	0.2270	505	0.0289	0.0131	2.00
7	ANALGESICS-- DERMATOLOGICAL_AGENTS	8519	0.12	3326	0.05	1.43	3973	0.2270	707	0.0404	0.0130	1.41
8	ANALGESICS-- CEPHALOSPORINS	8519	0.12	871	0.01	3.79	3973	0.2270	290	0.0166	0.0100	2.65
9	ANALGESICS-- PROTON_PUMP_INHIBITORS	8519	0.12	1429	0.02	2.69	3973	0.2270	315	0.0180	0.0092	2.26
10	ANALGESICS -- IRON_PRODUCTS	8519	0.12	1013	0.01	2.29	3973	0.2270	394	0.0225	0.0087	1.70
11	ANALGESICS-- MISCELLANEOUS_ANTIBIOTICS	8519	0.12	544	0.01	3.10	3973	0.2270	203	0.0116	0.0083	3.14

12	ANALGESICS--SEX_HORMONES	8519	0.12	4945	0.07	0.83	3973	0.2270	559	0.0319	0.0082	1.13
13	BRONCHODILATORS--PENICILLINS	2683	0.04	5593	0.08	1.76	723	0.0413	1591	0.0909	0.0081	2.16
14	BRONCHODILATORS--RESPIRATORY_INHALANT_PRODUCTS	2683	0.04	200	0.00	72.33	723	0.0413	63	0.0036	0.0075	50.7
15	ANALGESICS--BRONCHODILATORS	8519	0.12	2683	0.04	0.82	3973	0.2270	723	0.0413	0.0073	0.78
16	ANALGESICS--ANTIDEPRESSANTS	8519	0.12	2798	0.04	1.06	3973	0.2270	575	0.0329	0.0071	0.96
17	ANTIEMETIC/ANTIVERTIGO_AGENTS--ANALGESICS	724	0.01	8519	0.12	1.82	420	0.0240	3973	0.2270	0.0071	1.31
18	ANALGESICS--QUINOLONES	8519	0.12	393	0.01	3.61	3973	0.2270	141	0.0081	0.0066	3.63
19	MACROLIDE_DERIVATIVES--PENICILLINS	3357	0.05	5593	0.08	0.99	932	0.0532	1591	0.0909	0.0065	1.34
20	ADRENAL_CORTICAL_STEROIDS--ANALGESICS	781	0.01	8519	0.12	1.52	302	0.0173	3973	0.2270	0.0064	1.63
21	ANTIDEPRESSANTS--ANTICONSULSANTS	2798	0.04	1280	0.02	6.76	575	0.0329	505	0.0289	0.0062	6.50
22	ANALGESICS--LINCOMYCIN_DERIVATIVES	8519	0.12	178	0.00	8.31	3973	0.2270	64	0.0037	0.0061	7.32
23	ANTICONSULSANTS--ANALGESICS	1280	0.02	8519	0.12	1.91	505	0.0289	3973	0.2270	0.0059	0.90
24	ANALGESICS--LAXATIVES	8519	0.12	268	0.00	7.84	3973	0.2270	91	0.0052	0.0057	4.81
25	ANALGESICS--ANTIHYPERTENSIVE_COMBINATIONS	8519	0.12	1925	0.03	0.92	3973	0.2270	242	0.0138	0.0054	1.73
26	ANALGESICS--DIURETICS	8519	0.12	716	0.01	2.09	3973	0.2270	164	0.0094	0.0053	2.52
27	ANALGESICS--BETA--ADRENERGIC_BLOCKING_AGENTS	8519	0.12	0	0.00	0	3973	0.2270	0	0	0.0053	0
28	ANALGESICS--ADRENAL_CORTICAL_STEROIDS	8519	0.12	781	0.01	1.88	3973	0.2270	302	0.0173	0.0050	1.28
29	BRONCHODILATORS--LEUKOTRIENE_MODIFIERS	2683	0.04	457	0.01	27.03	723	0.0413	97	0.0055	0.0050	21.9
30	BRONCHODILATORS--MACROLIDE_DERIVATIVES	2683	0.04	3357	0.05	2.45	723	0.0413	932	0.0532	0.0050	2.28

* Occ-R here is occurrence Richness

** ER-R here is ER Richness

The pair **ANTIHYPERTENSIVE_COMBINATIONS -- CALCIUM_CHANNEL_BLOCKING_AGENTS**, which is Ranked 47 by ER visits, have much higher ER richness compared to its occurrence richness (16.44739 vs. 44.10178). On the other hand, the pair **ANALGESICS --MUSCLE_RELAXANTS** has higher occurrence richness and lower ER richness (30.89 vs. 19.77). This could mean that the pair **ANTIHYPERTENSIVE_COMBINATIONS --CALCIUM_CHANNEL_BLOCKING_AGENTS** jointly may be less safety than **ANALGESICS -- MUSCLE_RELAXANTS** even though the later occurred more frequently.

Figure 4.16 shows the richness of occurrence and the richness of ER visits values for TC1S1 drug class pairs and **Table 4.38** shows example pairs for TC1S1 classes with high occurrence richness and low ER richness, high occurrence richness and low ER richness, and low occurrence richness and high ER richness. Based on the richness results, only one TC1S1 class pair was found for the case (low occurrence richness and high ER richness).

Figure 4.16 Relationship between TC1S1 class pairs occurrence and ER richness. Logarithms are in base 10.

Table 4.38 Example of TC1S1 class pairs with high occurrence richness and low ER richness, high occurrence richness and low ER richness, and low occurrence richness and high ER richness.

	TC1S1 class pairs	ER- richness	Occ- Richness
high occurrence richness and high ER richness	MISCELLANEOUS_GENITOURINARY_TRACT_AGENTS--QUINOLONES	387.42	306.71
	ANTIDIURETIC_HORMONES--DIGESTIVE_ENZYMES	4,138.36	787.61
	ANTIRHEUMATICS--ANTIMETABOLITES	886.79	438.32
	CHOLINESTERASE_INHIBITORS--MISCELLANEOUS_CENTRAL_NERVOUS_SYSTEM_AGENT	413.83	795.56
	MISCELLANEOUS_CARDIOVASCULAR_AGENTS--MISCELLANEOUS_CENTRAL_NERVOUS_SYSTEM_AGENT	1,241.51	1,750.24
high occurrence richness and low ER richness	ANTICOAGULANTS--CALCITONIN	0	492.25
	(5_AMINOSALICYLATES)--ANTIMETABOLITES	0	345.25
	ADRENAL_CORTICAL_STEROIDS--CHOLINERGIC_AGNISTS	0	161.35
	ALKYLATING_AGENTS--ANTIADRENERGIC_AGENTS--PERIPHERALLY_ACTING	0	282.55
	AMEBICIDES--ANTHELMINTICS	0	203.25
	ANTIANGINAL_AGENTS--VASODILATORS	0	400.05
	ANTIARRHYTHMIC_AGENTS--CALCITONIN	0	316.62
	ANTIDIARRHEALS--ANTIRHEUMATICS	0	228.29
	ANTIHYPERURICEMIC_AGENTS--CHOLINESTERASE_INHIBITORS	0	238.67
	ANTIMALARIAL_AGENTS--CHOLINERGIC_AGNISTS	0	369.55
low occurrence richness and high ER richness	NASAL_PREPARATIONS--URINARY_ANTISPASMODICS	126.55	1.15

It is important to observe and compare how polypharmacy of TC1 drug class and polypharmacy of TC1S1 drug class flag and highlight risks. This helps people in health care fields to know which one is more reliable at certain health conditions. Thus, we compare the results obtained from the associations between both drug classes and ER visits. This involves their ranking based on ER visits, and their richness with respect to ER occurrence. **Table 4.39** shows few examples of single TC1 drug classes along with their original ranking based on ER visits for patients, some of TC1S1 pairs which individually form subclasses from the parent TC1 class as well as their original ranking based on the ER visits, and finally, the richness measure for TC1S1 class pairs.

From Table 4.39 we can observe that the single TC1 classes Respiratory agents and Anti-infectives are ranked by ER visits as 4 and 2 respectively. This means that these drug classes are associated with high risk according to the definition of TC1 drug class. However, if we consider the TC1S1 pairs, we can notice that the pair **BRONCHODILATORS--RESPIRATORY_INHALANT_PRODUCTS** has high ER richness while the pair **ANTIHISTAMINES--BRONCHODILATORS** has low ER richness even though they both are formed by combining TC1S1 subclasses (i.e., **BRONCHODILATORS**, **RESPIRATORY_INHALANT_PRODUCTS**, **ANTIHISTAMINES**, and **BRONCHODILATORS**) that belong to the same super TC1 class (**Respiratory agents**). The high richness for the pair **BRONCHODILATORS--RESPIRATORY_INHALANT_PRODUCTS** means that these drug classes together tend to have more association with ER than what is expected from the occurrence of individual subclasses. On the other hand, the low richness for the pair **ANTIHISTAMINES--BRONCHODILATORS** mean that these drug classes together tend to have much lower association with ER and considered to be relatively much safer. As a consequence, we can conclude here that even though TC1 single class (**Respiratory agents**) is flagged to be risky based on ER visits, the richness for its subclasses pairs indicates that the subclasses may not necessarily be at the same level of risk. The same argument apply for the case of (**Anti-infectives**) and the corresponding TC1S1 pairs:

- ANTITUBERCULOSIS_AGENTS--LINCOMYCIN_DERIVATIVES
- ANTIFUNGALS--LINCOMYCIN_DERIVATIVES
- ANTIMALARIAL_AGENTS--ANTIVIRAL_AGENTS

The reason behind this different estimates of risks is because TC1 drug classes are broad, general, and modeled classes compared to those for TC1S1. As a result, we can now infer that the TC1S1 approach to defining polypharmacy is more informative and provide a more detailed view of looking at more branched drug classes and their associations with health problems. **Table 4.41** shows the above Two TC1 classes along with their TC1S1 subclasses.

Table 4.39 Comparison of some single TC1 classes and some of their continent TC1S1 class pairs ranking based on ER visits along with the richness of the TC1S1 class pairs.

Single TC1 class	#ER/#Occ	Multiple TC1S1	#ER/#Occ	ER-Richness
Respiratory agents ranked 4 by ER.	0.25	BRONCHODILATORS-- RESPIRATORY_INHALANT_PRODUCTS (Ranked 16 by ER)	0.30	72.33
		ANTIHISTAMINES-- BRONCHODILATORS (ranked 67 by ER)	0.28	7.32
Anti-infectives ranked 2 by ER.	0.3	ANTITUBERCULOSIS_AGENTS-- LINCOMYCIN_DERIVATIVES 865	1	775.94
		ANTIFUNGALS-- LINCOMYCIN_DERIVATIVES 337	1	14.10
		ANTIMALARIAL_AGENTS-- ANTIVIRAL_AGENTS 714	0.5	3.30

Table 4.40 Two TC1 classes and their TC1S1 subclasses.

TC1 drug class Name	TC1S1 drug class Name
Respiratory agents	antihistamines antitussives bronchodilators decongestants expectorants miscellaneous respiratory agents respiratory inhalant products antiasthmatic combinations upper respiratory combinations leukotriene modifiers lung surfactants

Anti-infectives	amebicides anthelmintics antifungals antimalarial agents antituberculosis agents antiviral agents carbapenems cephalosporins leprostatics macrolide derivatives miscellaneous antibiotics penicillins quinolones sulfonamides tetracyclines urinary anti-infectives aminoglycosides lincomycin derivatives glycylcyclines
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Now, we will compare the estimate of risks for TC1 drug class and TC1S1 drug class for the case whereby the two TC1S1 classes forming a pair are originated from different two TC1 classes. **Table 4.41** shows three examples of TC1 drug class pairs along with their original ranking based on ER visits for patients and their ER richness and some of TC1S1 pairs which individually form subclasses from the two parent TC1 classes as well as their original ranking based on the ER visits, and finally, the richness measure for TC1S1 class pairs. It can be observed that even though the TC1 class pairs (**antineoplastics--miscellaneous agents**), (**cardiovascular agents--coagulation modifiers**), and (**central nervous system agents-- miscellaneous agents**) are ranked relatively low based on ER visits sort (92, 44, and 33, respectively), and have low ER richness using TC1 definition, they have high ER richness using TC1S1 definition. This indicates that a single TC1 drug class final ranking and richness could be affected by the results coming from so many subclasses embedded under this class, and so this emphasizes that using this type of drug classes may not

be an appropriate choice when we want an accurate, reliable, and more specific associations with health problems.

Table 4.41 Comparison of some TC1 class pairs and some of their continent TC1S1 class pairs ranking based on ER visits along with their richness values.

Parent TC1 pair	#ER/#Occ	ER-Richness	TC1S1 pair	#ER/#Occ	ER-Richness
antineoplastics -- miscellaneous agents (ranked 92 by ER)	1	16.26	ANTIRHEUMATICS-- ANTIMETABOLITES Ranked 154 By ER	0.16	886.79
cardiovascular agents -- coagulation modifiers (ranked 44 by ER)	0.3	6.68	ANTICOAGULANTS— VASODILATORS 156	0.6	730.3
central nervous system agents -- miscellaneous agents (ranked 33 by ER)	0.37	3.42	CHOLINESTERASE_INHIBITORS- -URINARY_ANTISPASMODICS	0.6	689.72

Table 4.42 summarizes top 20 ER richness ranked by the corresponding ER visits for patients to provide a comparative overview of the richness values for each definition.

Table 4.42: Summary of ER richness occurrence for the top 20 polypharmacy using each definition ranked by #ER visits.

Drug pairs	Drugs	Active ingredient pairs	AI	TC1 class Pairs	TC1	TC1S1 class Pairs	TC1S1
HYDROCO/APAP-- IBUPROFEN	13.15	ACETAMINOPHEN-- HYDROCODONE BITARTRATE	6133.93	Anti_infectives--Central nervous system agents	2.11	ANALGESICS-- MUSCLE_RELAXANTS	19.77
AMOXICILLIN-- IBUPROFEN	8.62	ACETAMINOPHEN-- CODEINE PHOSPHATE	0	Cardiovascular agents-- Metabolic agents	19.89	ANALGESICS--PENICILLINS	2.04
AMOXICILLIN-- HYDROCO/APAP	7.77	AMOXICILLIN-- CLAVULANATE POTASSIUM	0	Central nervous system agents-- Psychotherapeutic agents	6.44	ANALGESICS-- MACROLIDE_DERIVATIVES	2.25
APAP/CODEINE-- AZITHROMYCIN	40.44	ACETAMINOPHEN-- OXYCODONE HYDROCHLORIDE	213.13	Central nervous system agents--Cardiovascular agents	1.41	ANALGESICS-- ANTIEMETIC/ANTIVERTIGO_ AGENTS	3.10
ALBUTEROL-- AMOXICILLIN	1.55	SULFAMETHOXAZOLE-- TRIMETHOPRIM	0	Anti_infectives-- Respiratory agents	3.16	ADRENAL_CORTICAL_STERO IDS--BRONCHODILATORS	21.83
AMOXICILLIN-- AZITHROMYCIN	17.74	AMOXICILLIN-- IBUPROFEN	2.03	Central nervous system agents-- Hormones/hormone modifiers	1.76	ANALGESICS-- ANTICONVULSANTS	2.00
AZITHROMYCIN-- HYDROCO/APAP	4.71	HYDROCHLOROTHIAZID E--LISINOPRIL	54.59	Central nervous system agents--Gastrointestinal agents	3.51	ANALGESICS-- DERMATOLOGICAL_AGENTS	1.41
CYCLOBENZAPR-- HYDROCO/APAP	3.80	ALBUTEROL SULFATE-- PREDNISONE	10.90	Central nervous system agents--Respiratory agents	1.51	ANALGESICS-- CEPHALOSPORINS	2.65
CYCLOBENZAPR-- IBUPROFEN	11.21	AMOXICILLIN-- ALBUTEROL SULFATE	2.32	Anti_infectives--Topical agents	2.48	ANALGESICS-- PROTON_PUMP_INHIBITOR S	2.26
IBUPROFEN-- OXYCOD/APAP	20.84	ALBUTEROL SULFATE-- FLUTICASONE PROPIONATE	1.56	Cardiovascular agents-- Central nervous system agents	0.92	ANALGESICS -- IRON_PRODUCTS	1.70
IBUPROFEN-- PREDNISONE	8.46	CYCLOBENZAPRINE HYDROCHLORIDE-- IBUPROFEN	20.22	Central nervous system agents--Topical agents	1.26	ANALGESICS-- MISCELLANEOUS_ANTIBIOTI CS	3.14
AMLODIPINE-- LISINOPRIL	11.88	AZITHROMYCIN DIHYDRATE-- IBUPROFEN	11.12	Central nervous system agents--M Metabolic agents	1.59	ANALGESICS-- SEX_HORMONES	1.13
AZITHROMYCIN-- IBUPROFEN	40.44	IBUPROFEN-- PREDNISONE	1.28	Hormones/hormone modifiers--Respiratory agents	4.16	BRONCHODILATORS-- PENICILLINS	2.16

CLINDAMYCIN-- HYDROCO/APAP	1.55	AMLODIPINE BESYLATE-- -LISINAPRIL	5.98	Respiratory agents-- Topical agents	4.04	BRONCHODILATORS-- RESPIRATORY_INHALANT_P RODUCTS	50.70
AZITHROMYCIN-- PREDNISONE	17.74	AZITHROMYCIN DIHYDRATE-- PREDNISONE	28.04	Anti_infectives-- Hormones/hormone modifiers	1.64	ANALGESICS-- BRONCHODILATORS	0.78
APAP/CODEINE-- IBUPROFEN	4.71	ETHINYL ESTRADIOL-- NORETHINDRONE ACETATE	0.81	Central nervous system agents--Nutritional products	2.09	ANALGESICS-- ANTIDEPRESSANTS	0.96
HYDROCO/APAP-- PROMETHAZINE	3.80	ALBUTEROL SULFATE-- BUDESONIDE	3.58	Cardiovascular agents-- Gastrointestinal agents	4.61	ANTIEMETIC/ANTIVERTIGO_ AGENTS--ANALGESICS	1.31
LISINAPRIL-- SIMVASTATIN	11.21	CYCLOBENZAPRINE HYDROCHLORIDE-- NAPROXEN	0.00	Anti_infectives-- Cardiovascular agents	0.76	ANALGESICS--QUINOLONES	3.63
IBUPROFEN-- TRAMADOL HCL	20.84	IBUPROFEN-- TRAMADOL HYDROCHLORIDE	1.01	Cardiovascular agents-- Hormones/hormone modifiers	2.00	MACROLIDE_DERIVATIVES-- PENICILLINS	1.34
ALBUTEROL-- PREDNISONE	13.15	AMOXICILLIN-- AZITHROMYCIN DIHYDRATE	93.18	Cardiovascular agents-- Psychotherapeutic agents	3.10	ADRENAL_CORTICAL_STERO IDS--ANALGESICS	1.63

As observed from table 4.42, the polypharmacy of active ingredients seems to be more sensitive than other definitions for the richness measure. The richness of active ingredients may not necessarily align with the richness of the parent drugs. For example, the drug pair **(ALBUTEROL#AMOXICILLIN)** has drug-richness that is equal to 3.79 while the active ingredient pair **(AMOXICILLIN#ALBUTEROL SULFATE)** has AI- richness that is equal to 1.55. On the other hand, the richness for drug pair **(AMOXICILLIN#AZITHROMYCIN)** is 1.12898, but for AI richness, it decreased to 0.50 for the pair **(AMOXICILLIN#AZITHROMYCIN DIHYDRATE)**. Thus, these differentiation should be taken into consideration while studying polypharmacy health problems.

4.5 Automated thresholds for polypharmacy

The following sub sections provide tables and figures that shows and visualize the values of the Delta function (discussed previously in Chapter 3) for each polypharmacy category and discuss their results values.

4.5.1. Delta Function

As illustrated previously in Chapter 3, we define the Delta function as the difference in ER values between two thresholds as the following $\Delta(k, j) = \frac{(\frac{\#ER}{\#PP})_k - (\frac{\#ER}{\#PP})_j}{(\frac{\#ER}{\#PP})_j}$, and we consider a specific case of the delta function by which we estimate the change attributed to each threshold k and the threshold 1 assuming that ,using any polypharmacy definition, the association between single element and ER problems should be ideally the least. The percentage threshold can then be chosen by considering the variation of $\Delta(k, 1)$. A specific percentage increase of this measure can be chosen depending on the risk level that is desired to be investigated. We use 50% increase as an example here. In this section, we will use an exemplary case where we study 50% increase in the variation of $\Delta(k, 1)$ to determine the problematic thresholds for each definition. The results will be presented started by polypharmacy of drugs followed by polypharmacy of active ingredients followed by polypharmacy of drug classes. **Table 4.43** and **Figure 4.17** show the values of delta function for the drug-based polypharmacy definition, respectively.

k value	Y2011	Y2012	Y2013	Y2014	Y2015
1	0	0	0	0	0
2	0.189485	0.222993	0.220109	0.273258	0.299636
3	0.309234	0.345682	0.345899	0.328043	0.419536
4	0.497979	0.46116	0.485189	0.524823	0.610022
5	0.588648	0.615404	0.563554	0.626544	0.706004
6	0.635043	0.779675	0.7715	0.809136	1.026679
7	0.782341	0.902517	0.969403	0.970613	1.22419
8	0.874798	0.968218	1.177683	1.345501	1.454539
9	0.908378	1.10086	1.287882	1.420752	1.719018
10	1.464232	1.116019	1.498891	1.914181	1.95108
11	1.289863	1.609262	1.584395	1.573514	1.896542
12	1.783303	3.380951	2.535669	2.640168	2.590159
13	2.022353	2.608169	2.108939	1.830684	2.554512
14	2.058811	2.140507	1.878488	2.91856	3.930735
15	2.387897	2.936102	2.672032	2.239184	2.942776
16	2.46455	3.267935	3.878675	4.386803	3.977708

Table 4.43. Values of $\Delta(K,1)$ for drugs PP vs. ER measure for years (2011-2015)

Figure 4.17. Values of $\Delta(K,1)$ for drug PP vs. ER measure for years (2011-2015)

In general, the variation $\Delta(K,1)$ for drug polypharmacy increases with increasing number of threshold. This implies that polypharmacy with higher number of drugs (i.e., greater than 1) is likely to be associated with more ER problems. In particular, $\Delta(K,1)$ is less than 1 for the thresholds (1-5), ranges from 1 to around 2.5 for thresholds (6-13), and nearly about 2.6 to 3 for thresholds (14-16). Also, it can be observed from figure 4.17 that the variation $\Delta(K,1)$ has an overall increase over time from 2011 to 2015.

Table 4.44 and **figure 4.18** show the values of delta function for the polypharmacy of active ingredients.

k value	Y2011	Y2012	Y2013	Y2014	Y2015
1	0	0	0	0	0
2	0.166546	0.219991	0.156289	0.259154	0.29883
3	0.363161	0.323095	0.39805	0.381356	0.507789
4	0.383793	0.449688	0.416232	0.505856	0.584702
5	0.694256	0.48364	0.655249	0.704404	0.808144
6	0.718104	0.674156	0.684001	0.84031	1.007899
7	0.8081	0.976339	0.985538	0.886392	1.251168
8	0.793464	1.022654	1.083476	1.177541	1.416201
9	1.006683	1.140404	1.029003	1.538357	1.755961
10	0.936848	8.555351	1.24804	1.699281	2.018783
11	1.721268	1.285563	1.558277	1.573989	2.062994
12	1.256805	1.948508	2.22967	1.907854	2.271668
13	2.206634	1.948039	1.79316	2.639904	2.57344
14	1.688903	2.326416	2.387203	2.6276	3.212641
15	2.014106	1.893232	2.235541	2.557164	3.881116
16	2.879682	2.875826	3.405001	3.538909	3.915724

Table 4.44. Values of $\Delta(K,1)$ for active ingredient PP vs. ER measure for years (2011-2015)

Figure 4.18. Values of $\Delta(K,1)$ for active ingredients PP vs. ER measure of years (2011-2015)

The variation $\Delta(K,1)$ for active ingredient polypharmacy shows similar tendency to the variation estimates for drug polypharmacy. Similar to drug polypharmacy, polypharmacy with higher number of active ingredients (i.e., greater than 1) is likely to be associated with more ER problems. Also, figure 4.18 shows that the variation $\Delta(K,1)$ tend to increase over time from 2011 to 2015. The greatest value for $\Delta(K,1)$ is 8.5, which was found for $k=10$ in 2012. This is because the ER visits found for this threshold were much higher than the number of polypharmacy ($\#ER=630$, $\#PP=296$). Some of the reported ER visits were relatively high for about 8 patients (e.g., 8,7,6, or 5 visits per year). Thus, the resulting ratio ($\#ER/\#PP$) for this threshold is very high

compared to the others in 2012 and in all years. **Table 4.45** and **Figure 4.19** show the values of delta function for the polypharmacy of TC1 drug classes.

k value	Y2011	Y2012	Y2013	Y2014	Y2015
1	0	0	0	0	0
2	0.185875	0.207333	0.187966	0.23479	0.18153
3	0.410034	0.419495	0.410904	0.387031	0.417995
4	0.473965	0.57439	0.702658	0.683705	0.706127
5	0.67914	0.945249	0.983808	1.09742	1.144057
6	1.161659	1.14829	1.231444	1.293912	1.729688
7	1.519644	1.489975	1.708219	1.860121	2.091849
8	2.365361	2.184118	1.996787	1.88839	2.822632
9	2.713373	2.606817	2.536552	3.502504	2.691316
10	1.500583	4.205949	4.696988	4.38011	3.003476
11	0.804932	2.354696	2.113945	6.765674	5.764784
12	5.317263	1.477314	12.70136	2.663054	2.927939
13	-1	#DIV/0!	6.473468	-1	-1
14	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
15	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
16	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!

Table 4.45. Values of $\Delta(K,1)$ for TC1 class PP vs. ER measure of years (2011-2015)

Figure 4.19. Values of $\Delta(K,1)$ for TC1 class PP vs. ER measure of years (2011-2015)

From Table 4.45 and Figure 4.19 we can observe that increasing number of TC1 classes has positive relationship with number of emergency room admissions at the threshold range (2-10). However, for thresholds higher than 10 and less than 14 the results were fluctuated. This is explained given that there are much less polypharmacy groups for these thresholds (i.e., as thresholds increase, the number of polypharmacy sets found for these thresholds decrease). As a result to this fact, no polypharmacy sets were found for thresholds greater than 14. The noticeable increase located for 2013 in Figure 4.19 is because there was one patient who has 6 visits and three polypharmacy sets. This contributes to increase the #ER total to be 22 vs. 6 for #PP polypharmacy sets and increase the final variation for $\Delta(K,1)$ to be about 12.70. **Table 4.46** and **Figure 4.20** show the values of delta function for the polypharmacy of TC1 drug classes.

k value	Y2011	Y2012	Y2013	Y2014	Y2015
1	0	0	0	0	0
2	0.180859	0.223334	0.21779	0.25446	0.273589
3	0.35387	0.354538	0.325613	0.293121	0.362164
4	0.505949	0.412752	0.424582	0.453412	0.618185
5	0.569774	0.645759	0.71072	0.672864	0.691822
6	0.564856	0.842779	0.838142	0.902014	1.147886
7	0.81046	0.232098	1.121623	1.107839	1.317363
8	1.053506	0.946379	1.139427	1.75915	1.631853
9	1.40176	1.180292	1.407035	1.778943	2.008079
10	1.722948	1.581156	2.347312	1.370593	2.07888
11	1.410364	2.331826	1.824076	2.288293	2.337432
12	2.312381	2.346753	2.541634	2.629673	3.323839
13	2.463039	2.896342	2.872186	2.554303	3.472542
14	2.376703	3.839667	3.477216	4.016547	4.281758
15	2.809931	3.052196	3.592593	3.957821	2.465002
16	2.280774	3.826716	3.709416	4.236249	4.030709

Table 4.46. Values of $\Delta(K,1)$ for TC1S1 class PP vs. ER measure of years (2011-2015)

Figure 4.20. Values of $\Delta(K,1)$ for TC1S1 class PP vs. ER measure for years (2011-2015).

The variation $\Delta(K,1)$ for TC1S1 polypharmacy generally have similar trend to that for active ingredient. In particular, #ER visits increase with increasing number of thresholds so polypharmacy with higher number of drug classes of this type (i.e., greater than 1) is likely to be associated with more ER problems. Also, the overall increase in the variation $\Delta(K,1)$ over time from 2011 to 2015 persists for this polypharmacy definition as shown in Figure 4.20.

We then calculate the average value for every year to get an overall view of the values over time. **Table 4.47** contains the numerical values while **Figure 4.21** show the graph of these values.

k value	AI-Avg	Drug-Avg	TC1-Avg	TCS1-Avg
1	0	0	0	0
2	0.2185	0.24187	0.200032	0.223244
3	0.39382	0.350566	0.411483	0.330026
4	0.469048	0.51712	0.639817	0.474692
5	0.669855	0.621935	0.989507	0.654086
6	0.78378	0.808919	1.330563	0.860198
7	0.987717	0.978749	1.76991	0.856638
8	1.11348	1.189678	2.288172	1.336593
9	1.300614	1.314252	2.894918	1.567383
10	2.190311	1.62676	3.88247	1.818723
11	1.644473	1.612296	4.092853	2.055386
12	1.946854	2.589814	5.441164	2.668355
13	2.242127	2.219799	0.96377	2.863218
14	2.495532	2.67264	#DIV/0!	3.742511
15	2.503638	2.646897	#DIV/0!	3.240996
16	3.387051	3.769143	#DIV/0!	3.810177

Table 4.47. Average values of $\Delta(K,1)$ for all PP vs. ER measure of years (2011-2015).

Figure 4.21. Values of $\Delta(K,1)$ for all PP vs. ER measure of years (2011-2015)

We can observe from Table 4.42 and Figure 4.21 that defining polypharmacy using the number of TC1 class shows the highest the average followed by the average for the definition that uses TC1S1 Followed by the average for the definition that uses drugs, and finally the average for the definition that uses active ingredients. This implies that the definition with higher level of granularity provides more specific results than the definition with lower level of granularity. As a result, defining the polypharmacy using active ingredients as the basic type should provide superior and more related associations, followed by polypharmacy of drugs followed by polypharmacy of TC1S1 drug classes, and finally polypharmacy of TC1 drug classes.

4.5.2 Choosing Polypharmacy Thresholds

Section 4.5.1 provides the values of our proposed function Δ with respect to the threshold 1 assuming that this threshold (which represents single drug/single active ingredient/single drug class) should be associated to the least risk in comparison to any threshold greater than 1. **Table 4.48** summarizes the average differences, showing where they crossed above 50% increase. We use these values to derive the polypharmacy thresholds based on the above assumption.

Table 4.48 Summary statistics on the values for the delta function ($\Delta(K,1)$), and the minimum k value at which $\Delta(K,1) \geq 0.50$.

	k value	Y2011	Y2012	Y2013	Y2014	Y2015	AvgY11-Y15
AI	5	0.694	0.484	0.655	0.704	0.808	0.669
	Avg	1.176	1.742	1.351	1.523	1.838	1.526
	std	0.772	2.045	0.908	0.978	1.171	0.983
TC1S1	5	0.570	0.646	0.711	0.673	0.692	0.658
	avg	1.388	1.648	1.770	1.885	2.003	1.739
	stdv	0.887	1.299	1.236	1.366	1.315	1.190
Drug	4	0.498	0.461	0.485	0.525	0.610	0.516
	Avg	1.217	1.497	1.465	1.587	1.820	1.517
	stdev	0.765	1.091	1.016	1.126	1.184	1.005
TC1	4	0.474	0.574	0.703	0.684	0.706	0.628
	Avg	1.557	1.601	2.661	2.251	2.135	2.041
	Stddev	1.483	1.173	3.557	1.979	1.590	1.547

As a result, we can infer that the thresholds values are 4 drugs, 5 active ingredients, 4 TC1 classes, and 5 TC1S1 classes. Thus, we can substitute the thresholds we defined in chapter3 for our composite approach to define polypharmacy as the following:

$k_{\Delta} = 4$ for drugs, $k_{\Delta I} = 5$ for active ingredients, $k_{\Delta c} = 4$ if we use TC1 drug class definition or $k_{\Delta c} = 5$ if we use TC1S1 class definition.

4.5.3 Redefining polypharmacy

Now, we apply the joint consideration of the three criteria, this include:

- Strict polypharmacy definition (Using AND Logic on the three definitions)
By which we obtain the following definitions:
 - drug and AI and TC1 (here, AI=Active Ingredients)
 - drug and AI and TC1S1
- Less strict polypharmacy definition (Using OR Logic on the three definitions), this includes:
 - Meeting 1 criteria of the three.
 - drug OR AI
 - drug OR TC1
 - drug OR TC1S1
 - AI OR TC1
 - AI OR TC1S1
 - drug OR AI OR TC1
 - drug OR AI OR TC1S1
 - Meeting 2 criteria of the three (with at most one of the drug class thresholds), this includes:
 - drug and AI
 - drug and TC1
 - drug and TC1S1
 - AI and TC1
 - AI and TC1S1

Table 4.49 provides the values of ER visits, the number of polypharmacy sets found in the specified thresholds, and the ratio #ER/#PP for each definition. **Figure 4.22** shows a comparative bar graph for these definitions.

Table 4.49 Measuring #ER/#PP for all possible definitions of polypharmacy

Definition	ER sum	PP sum	#ER/#PP
drug	31271	66566	0.470
AI	27876	56082	0.497
TC1	20867	39920	0.523
TCS1	21772	41267	0.528
drug and AI and TC1	128789	234428	0.549
drug and AI and TC1S1	139857	260308	0.537
drug and AI	64802	128048	0.506
drug and TC1	51409	96796	0.531
drug and TC1S1	54396	102525	0.531
AI and TC1	51828	96464	0.537

AI and TC1S1	52313	97661	0.536
drug OR AI OR TC1	80014	162568	0.492
drug OR AI OR TC1S1	80919	163915	0.494
drug OR AI	59147	122648	0.482
drug OR TC1	52138	106486	0.490
drug OR TC1S1	53043	107833	0.492
AI OR TC1	48743	96002	0.508
AI OR TC1S1	49648	97349	0.510

Figure 4.22. compares #ER/#PP for all possible definitions of polypharmacy

As illustrated by figure 4.22, The composite definitions have the highest values of #ER/#PP. This means that with respect to safety, patients that meet the three criteria jointly, (i.e, satisfy the thresholds for the definitions: drug and AI and TC1, OR the definition: drug and AI and TC1S1) may expose to significantly higher risk, when compared with patients who meet the individual definitions of polypharmacy or the relatively relaxed ones (joint by logical OR).

On the other hand, this should not eliminate the importance of the definitions formed by the logical OR since these definitions may provide additional details that could be missed when considering one individual definition. In particular, health care professional may need to highlight patients profile of polypharmacy who (not strictly) happened to meet more than a criterion rather than looking at it from one angle.

For instance, consider a patient is taking two drugs (**Bacitracin**, and **EPIDUO FORTE**). This person does not have a polypharmacy by considering the classic drug definitions and setting its threshold k_{Δ} to be three or more (i.e., $k_{\Delta}=3$). Likewise, these drugs belong to one drug class (**DERMATOLOGICAL AGENTS**) as classified by TC1S1 therapeutic classes and so this person will not have a polypharmacy if we set the threshold for this definition $k_{\Delta c}$ to be say (four or more) (i.e., $k_{\Delta c}=4$). Looking at this polypharmacy from either a drug point or a TC1S1 classification point

of view will not flag any risk. However, considering the active ingredient approach, these two drugs contains 5 ingredients namely (**ADAPALENE, BENZOYL PEROXIDE, BACITRACIN ZINC, NEOMYCIN SULFATE, and POLYMYXIN B SULFATE**). As a result, if we use the threshold 5 for this definition (i.e., $k_{AI}=5$), this person will have a polypharmacy using the active ingredient definition. Based on the above example, the following definitions will not capture the polypharmacy and so may not be effective enough in preventing any possibility of risk:

- **drug and AI and TC1S1**
- **drug and AI**
- **drug and TC1S1**
- **AI and TC1S1**
- **drug OR TC1S1**
- **drug**
- **TC1S1**

On the other hand, these definitions will capture this polypharmacy:

- **drug OR AI OR TC1S1**
- **drug OR AI**
- **AI OR TC1S1**
- **AI**

Another example is a patient taking the four drugs (**ZOVIRAX, LASTACFT, XANAX, and SAPHRIS**). These drugs contains the four active ingredients (**ACYCLOVIR, ALCAFTADINE, ALPRAZOLAM, ASENAPINE MALEATE**) and belong to the classes (**DERMATOLOGICAL AGENTS, OPHTHALMIC PREPARATIONS, ANXIOLYTICSEDATIVESAND HYPNOTICS, and ANTIPSYCHOTICS**) as classified by TC1S1 classification scheme. Now, if we keep our thresholds choice as the example above (i.e., $k_{\Delta}=3$, $k_{\Delta c}=4$, and $k_{AI}=5$ for drugs, TC1S1 drug class, active ingredients respectively) , this patient will have polypharmacy based on drug definition and TC1S1 definition but not by the active ingredient definition.

Thus, the definitions that will capture the polypharmacy this time are:

- **drug OR AI OR TC1S1**
- **drug and TC1S1**
- **drug OR TC1S1**
- **AI OR TC1S1**
- **drug OR AI**
- **drug**
- **TC1S1**

and the ones that will not do so are:

- **drug and AI and TC1S1**
- **drug and AI**
- **AI and TC1S1**
- **AI**

Therefore, and based on the above examples, we can infer that allowing the **logical OR** that join the polypharmacy of (drug and AI) or (TC1S1 and AI) would facilitate better observing for polypharmacy issues involved. In fact, enabling the OR logic on the **three definitions** would provide the safest consideration of risk even though it could be too loose to capture many polypharmacy sets as risky when they could not necessarily be in the reality. Yet, in general, it would be better not to miss any potential risk (using the OR logic) than waiting to reach high risk by meeting the three criteria (using the AND logic).

We here emphasize that the choice among these different approaches to polypharmacy could depend on the specific application and the risk that the health care specialists think is appropriate for patients.

Chapter 5: Conclusion

In this study, we have used three methods to define polypharmacy including polypharmacy of drugs and polypharmacy of drug-classes, which have been considered in prior work, as well as our proposed definition by the drug active ingredients. Independent of these definitions, our results indicated a general increase in polypharmacy problems reflected by ER visits with increasing number of drugs/drug classes/or active ingredients. However, the threshold found for those polypharmacy varied with the specific basic elements used in the definition. This variation resulted in our idea of defining polypharmacy in a composite manner by combining three criteria that determine the thresholds for each definition. Our results also included quantitative analysis of the occurrence of single-elements (e.g., single drugs, single drug classes, or single active ingredients), and the co-occurrence of multiple elements of the same basic type (e.g., two-drugs, two drug classes, two active ingredients, three-drugs, three drug classes, three active ingredients, etc.). This provides a basis for future studies to further analyze the incidences of common drugs, active ingredients, drug class polypharmacy combinations, as well as their richness to advance the study of their implications on patient's safety. In conclusion, this work forms a framework for healthcare specialists to observe the impact of each polypharmacy definition and their respective associations with emergency room (ER) visits, and which combinations of drugs, of drug classes, or of active ingredients are likely to result in significant hospitalization, and thus should be avoided.

The following are Key points summarizes the contributions from this work:

- If we must use one element to define polypharmacy, then active ingredients should be used.
- If we must use a drug class to define polypharmacy, then TC1S1 should be used.
- Whichever element type is used, we have proposed an automated way to determine the thresholds.

- For strict polypharmacy definition, we should use the AND logic on the different elements using the proposed thresholds.
- For less strict definition, we use the OR logic.
- Analysis of the richness or overrepresentation of the polypharmacy elements showed that the richness of ER occurrence with polypharmacy when considered with the direct polypharmacy occurrence richness provides a more insight on the association between polypharmacy and health problems.

5.1 Limitations

- Our assumption that patients actually take all medications they were prescribed pose a limitation as this may not hold at all times.
- The method used to extract active ingredients depends on exact matching of NDCs and drug names. Drug names are not necessarily consistent within the two dataset (i.e., MEPS dataset and NHANES dataset) used for this study. As a result, many active ingredients were not found and were substituted by drug NDC in the polypharmacy of ingredients. This would affect the results of polypharmacy of active ingredients with respect to the number of elements and the actual polypharmacy components.
- ER visits extracted from MEPS files represents the total ER visits for a patient within the MEPS year. In particular, there is no indication that those ER visits happened prior or later than the polypharmacy sets found in the rounds. Thus, whether the polypharmacy caused or (is caused by) the ER visits is unknown.

5.2 Future Work

The possible directions for future work can be listed as follows:

- Practitioners can study risk stratification of patients based on our methodology of determining polypharmacy thresholds. For example, further experiments can be done on thresholds of the three definitions of polypharmacy and their associations with specific health outcomes, such as specific chronic diseases.
- This work will benefit researchers who are interested in studying polypharmacy safety to prioritize the most common combinations of elements (two-drugs, two drug classes, two active ingredients, three-drugs, three drug classes, three active ingredients, etc) in their subsequent studies and consequently drive observations that are more connected to the majority of community problems. Another direction with the provided repository is mapping drugs to possible diseases and summarize the comorbidities that reflect the trends in the prescription claims data.
- Examine the list of elements involved in each polypharmacy definition against data sets of adverse drug events and drug interactions to determine whether they are potential to cause inappropriate therapy problems and create models by which the suspicious patterns of medications can be learned using data mining techniques.
- Involve patients' characteristics such as ethnicity, sex, and age to observe associations with regard to demographics.

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Appendices

A TC1S1 Class Codes and Names

Class Code	Class Name
-1	INAPPLICABLE
2	AMEBICIDES
3	ANTHELMINTICS
4	ANTIFUNGALS
5	ANTIMALARIAL AGENTS
6	ANTITUBERCULOSIS AGENTS
7	ANTIVIRAL AGENTS
9	CEPHALOSPORINS
10	LEPROSTATICS
11	MACROLIDE DERIVATIVES
12	MISCELLANEOUS ANTIBIOTICS
13	PENICILLINS
14	QUINOLONES
15	SULFONAMIDES
16	TETRACYCLINES
17	URINARY ANTI-INFECTIVES
18	AMINOGLYCOSIDES
19	ANTIHYPERLIPIDEMIC AGENTS
21	ALKYLATING AGENTS
23	ANTIMETABOLITES
24	ANTINEOPLASTIC HORMONES
25	MISCELLANEOUS ANTINEOPLASTICS
26	MITOTIC INHIBITORS
27	RADIOPHARMACEUTICALS
34	IN VIVO DIAGNOSTIC BIOLOGICALS
36	RECOMBINANT HUMAN ERYTHROPOIETINS
42	ANGIOTENSIN CONVERTING ENZYME INHIBITORS
43	ANTIADRENERGIC AGENTS PERIPHERALLY ACTING
44	ANTIADRENERGIC AGENTS CENTRALLY ACTING
45	ANTIANGINAL AGENTS
46	ANTIARRHYTHMIC AGENTS
47	BETA-ADRENERGIC BLOCKING AGENTS
48	CALCIUM CHANNEL BLOCKING AGENTS
49	DIURETICS
51	MISCELLANEOUS CARDIOVASCULAR AGENTS
53	VASODILATORS
54	VASOPRESSORS
55	ANTIHYPERTENSIVE COMBINATIONS

56	ANGIOTENSIN II INHIBITORS
58	ANALGESICS
64	ANTICONSULTANTS
65	ANTIEMETIC/ANTIVERTIGO AGENTS
66	ANTIPARKINSON AGENTS
67	ANXIOLYTICSEDATIVESAND HYPNOTICS
71	CNS STIMULANTS
73	MUSCLE RELAXANTS
80	MISCELLANEOUS CENTRAL NERVOUS SYSTEM
82	ANTICOAGULANTS
83	ANTIPLATELET AGENTS
85	MISCELLANEOUS COAGULATION MODIFIERS
88	ANTACIDS
90	ANTIDIARRHEALS
91	DIGESTIVE ENZYMES
92	GALLSTONE SOLUBILIZING AGENTS
94	H2 ANTAGONISTS
95	LAXATIVES
96	MISCELLANEOUS GI AGENTS
98	ADRENAL CORTICAL STEROIDS
99	ANTIDIABETIC AGENTS
101	SEX HORMONES
103	THYROID HORMONES
104	IMMUNOSUPPRESSIVE AGENTS
106	ANTIDOTES
107	CHELATING AGENTS
110	MISCELLANEOUS UNCATEGORIZED AGENTS
112	RADIOCONTRAST AGENTS
116	IRON PRODUCTS
117	MINERALS AND ELECTROLYTES
119	VITAMINS
120	VITAMIN AND MINERAL COMBINATIONS
121	INTRAVENOUS NUTRITIONAL PRODUCTS
123	ANTIHISTAMINES
124	ANTITUSSIVES
125	BRONCHODILATORS
127	DECONGESTANTS
128	EXPECTORANTS
129	MISCELLANEOUS RESPIRATORY AGENTS
130	RESPIRATORY INHALANT PRODUCTS
131	ANTIASTHMATIC COMBINATIONS
132	UPPER RESPIRATORY COMBINATIONS

134	ANORECTAL PREPARATIONS
135	ANTISEPTIC AND GERMICIDES
136	DERMATOLOGICAL AGENTS
146	MOUTH AND THROAT PRODUCTS
147	OPHTHALMIC PREPARATIONS
148	OTIC PREPARATIONS
150	STERILE IRRIGATING SOLUTIONS
151	VAGINAL PREPARATIONS
192	ANTIRHEUMATICS
194	ANTIGOUT AGENTS
219	NUTRACEUTICAL PRODUCTS
220	HERBAL PRODUCTS
240	LINCOMYCIN DERIVATIVES
243	LEUKOTRIENE MODIFIERS
247	NASAL PREPARATIONS
249	ANTIDEPRESSANTS
251	ANTIPSYCHOTICS
253	ANOREXIANTS
263	IMPOTENCE AGENTS
264	URINARY ANTISPASMODICS
265	URINARY PH MODIFIERS
266	MISCELLANEOUS GENITOURINARY TRACT AGENTS
272	PROTON PUMP INHIBITORS
277	5-AMINOSALICYLATES
284	VISCOSUPPLEMENTATION AGENTS
288	5-ALPHA-REDUCTASE INHIBITORS
289	ANTIHYPERURICEMIC AGENTS
293	GLUCOSE ELEVATING AGENTS
295	GROWTH HORMONES
303	AGENTS FOR PULMONARY HYPERTENSION
312	CHOLINERGIC AGONISTS
313	CHOLINESTERASE INHIBITORS
320	SMOKING CESSATION AGENTS
340	ALDOSTERONE RECEPTOR ANTAGONISTS
342	RENIN INHIBITORS
354	H. PYLORI ERADICATION AGENTS
355	FUNCTIONAL BOWEL DISORDER AGENTS
359	PERIPHERALLY ACTING ANTI OBESITY AGENTS
378	DRUGS USED IN ALCOHOL
397	MULTIKINASE INHIBITORS
398	BCR-ABL TYROSINE KINASE INHIBITORS
404	EGFR INHIBITORS

405	HER2 INHIBITORS
409	BONE RESORPTION INHIBITORS
411	CALCITONIN
412	UTEROTONIC AGENTS
413	ANTIGONADOTROPIC AGENTS
414	ANTIDIURETIC HORMONES
418	PARATHYROID HORMONE AND ANALOGS
419	GONADOTROPIN-RELEASING HORMONE ANTAGONIST
422	ANTITHYROID AGENTS
426	SYNTHETIC OVULATION STIMULANTS
437	IMMUNOSTIMULANTS

B Associations of polypharmacy results with ER

Table 1: Top 30 single drugs in the dataset ranked by the corresponding ER visits

		Number of ER					ER	
	Single drug	2011	2012	2013	2014	2015	Total	#ER/#occ
1	AMOXICILLIN	199	251	253	261	226	1,190	0.266
2	AZITHROMYCIN	210	243	216	183	39	891	0.280
3	HYDROCO/APAP	148	145	126	162	117	698	0.564
4	IBUPROFEN	112	140	138	149	152	691	0.413
5	APAP/CODEINE	67	59	83	50	45	304	0.495
6	LISINOPRIL	66	46	69	70	40	291	0.168
7	ALBUTEROL	34	73	68	51	49	275	0.350
8	CEPHALEXIN	40	28	50	51	27	196	0.364
9	PREDNISONE	32	42	45	48	23	190	0.436
10	AMOX/K CLAV		23	40	34	90	187	0.386
11	LEVOTHYROXIN	24	47	30	36	40	177	0.104
12	OXYCOD/APAP	30	41	25	33	46	175	0.540
13	NAPROXEN	31	26	40	33	44	174	0.353
14	ONDANSETRON	19	28	45	46	29	167	0.658
15	OMEPRAZOLE	19	36	37	34	28	154	0.214
16	PRENATAL	25	33	36	28	3	125	0.463
17	CYCLOBENZAPR	29	19	25	21	28	122	0.469
18	OXYCODONE	15	28	20	33	19	115	0.545
19	METFORMIN	35	32	11	12	24	114	0.146
20	PROAIR HFA		22	40	25	26	113	0.251
21	TRAMADOL HCL		27	18	32	33	110	0.444
22	SIMVASTATIN	19	25	20	22	20	106	0.105
23	CIPROFLOXACN	17	21	24	16	24	102	0.338
24	RANITIDINE	16	36	14	19	14	99	0.303
25	SERTRALINE	29	12	22	22	12	97	0.180
26	PENICILLN VK		17	24	36	17	94	0.349
27	CITALOPRAM	24	17	25	15	9	90	0.200
28	HYDROCHLOROT	10	18	17	17	23	85	0.184
29	PROMETHAZINE	27	18	20	12	8	85	0.455
30	METHYLPHENID	3	30	15	17	17	82	0.118

Table 2: Top 30 two-drug polypharmacy ranked by ER visits

		Number of ER					ER	
	Polypharmacy of two-drugs	2011	2012	2013	2014	2015	Total	#ER/#Occ
1	HYDROCO/APAP--IBUPROFEN	13	29	14	58	33	147	0.835
2	AMOXICILLIN--IBUPROFEN	16	18	26	14	20	94	0.320
3	AMOXICILLIN--HYDROCO/APAP	10	6	19	17	12	64	0.408
4	APAP/CODEINE--AZITHROMYCIN	8	19	20	9	0	56	0.483
5	ALBUTEROL--AMOXICILLIN	10	13	9	13	11	56	0.667
6	AMOXICILLIN--AZITHROMYCIN	16	3	16	13	6	54	0.563
7	AZITHROMYCIN--HYDROCO/APAP	7	18	7	14	7	53	0.639
8	CYCLOBENZAPR--HYDROCO/APAP	11	5	4	18	14	52	0.675
9	CYCLOBENZAPR--IBUPROFEN	5	15	10	8	12	50	0.610
10	IBUPROFEN--OXYCOD/APAP	6	9	16	11	5	47	0.701
11	IBUPROFEN--PREDNISONE	1	0	3	42	0	46	3.286
12	AMLODIPINE--LISINOPRIL	4	5	1	16	17	43	0.301
13	AZITHROMYCIN--IBUPROFEN	8	9	8	15	3	43	0.358
14	CLINDAMYCIN--HYDROCO/APAP	3	9	9	11	11	43	1.049
15	AZITHROMYCIN--PREDNISONE	5	7	12	5	7	36	0.571
16	APAP/CODEINE--IBUPROFEN	9	0	6	10	11	36	0.750
17	HYDROCO/APAP--PROMETHAZINE	7	6	3	11	3	30	1.304
18	LISINOPRIL--SIMVASTATIN	10	6	3	5	5	29	0.131
19	IBUPROFEN--TRAMADOL HCL		9	3	6	11	29	1.115
20	ALBUTEROL--PREDNISONE	10	10	2	3	3	28	0.875
21	CYCLOBENZAPR--NAPROXEN	3	7	10	6	1	27	0.409
22	ALBUTEROL--AZITHROMYCIN	12	4	3	3	4	26	0.441
23	HYDROCO/APAP--PENICILLN VK		3	10	7	6	26	0.491
24	AMOXICILLIN--PREDNISONE	4	1	5	15	1	26	0.542
25	AMLODIPINE--HYDROCHLOROT	1	6	3	8	5	23	0.240
26	CEPHALEXIN--HYDROCO/APAP	9	7	4	3	0	23	0.451
27	AMOXICILLIN--APAP/CODEINE	4	1	11	3	3	22	0.349
28	SERTRALINE--TRAZODONE	1	7	0	13	0	21	0.840
29	HYDROCO/APAP--NAPROXEN	2	4	4	7	3	20	0.541
30	HYDROCO/APAP--OXYCOD/APAP	0	5	7	7	1	20	0.800

Table 3: Top 30 three-drug polypharmacy ranked by ER visits

	Polypharmacy of three-drugs	Number of ER					ER	#ER/# occ
		2011	2012	2013	2014	2015	Total	
1	CYCLOBENZAPR--HYDROCO/APAP-- IBUPROFEN	5	3	9	3	7	27	0.931
2	ATENOLOL--CARISOPRODOL-- HYDROCHLOROT			24			24	24
3	IBUPROFEN--LANTUS--OMEPRazole		10	11			21	10.5
4	AMLODIPINE--METOPROLOL-- VALSART/HCTZ			12	0		12	2.4
5	DIVALPROEX--LEVETIRACETA-- OXCARBAZEPIN			12			12	4
6	CLINDAMYCIN--CYCLOBENZAPR-- OXYCODONE			12			12	12
7	GLIPIZIDE--LISINOPRIL--METFORMIN	2	0	5	0	4	11	0.333
8	ALBUTEROL--AMOXICILLIN-- PREDNISONE	4		7	0	0	11	2.2
9	AMOXICILLIN--HYDROCO/APAP-- IBUPROFEN	3	0	6	1	0	10	0.5
10	APAP/CODEINE--AZITHROMYCIN-- IBUPROFEN	0	10	0	0		10	1.666
11	CEPHALEXIN--HYDROCO/APAP-- IBUPROFEN			1	9		10	2
12	MIRTAZAPINE--PRAVASTATIN-- TERAZOSIN		2	8			10	3.333
13	LISINOPRIL--PERCOCET-- SIMVASTATIN		10				10	10
14	AMOXICILLIN--APAP/CODEINE-- IBUPROFEN	0	3	4	2	0	9	1
15	FEXOFENADINE--LEVETIRACETA-- VITAMIN D		9				9	3
16	AMOX/K CLAV--HYDROMORPHON-- NEXIUM			9			9	9
17	ALBUTEROL--QVAR-- TRAMADOL_HCL	9					9	9
18	ALBUTEROL--AZITHROMYCIN-- PREDNISOLONE	2	2	4	0	0	8	0.727
19	AZITHROMYCIN--PREDNISONE-- VENTOLIN HFA		0	3	0	5	8	1.142
20	HYDROCO/APAP--IBUPROFEN-- OXYCOD/APAP	2			2	4	8	1.6
21	AMLODIPINE--HYDROCO/APAP-- LISINOPRIL		2	6	0		8	1.6
22	ALBUTEROL--FLOVENT DISK-- PREDNISONE		8	0	0		8	2
23	CARISOPRODOL--IBUPROFEN-- PROMETHAZINE					8	8	4
24	ALPRAZOLAM--FOLIC_ACID-- HYDROCO/APAP	8					8	4

25	ALBUTEROL--AMOX/K CLAV-- PREDNISONE					8	8	4
26	ACETAMINOPHEN TAB 500 MG-- ATORVASTATIN--PROPRAN/HCTZ				8		8	4
27	HYDROXYZ HCL--RANITIDINE-- TRAZODONE		8				8	8
28	HYDROCOD/HOM--LISINOPRIL-- QUETIAPINE			8			8	8
29	ESCITALOPRAM--ONDANSETRON-- OXYCODONE				8		8	8
30	DICLOFENAC--HYDROCHLOROT-- RANITIDINE	8					8	8

Table 4: Top 30 single ingredients in the dataset ranked by ER visits

		Number of ER					Occ	ER	#ER/ #Occ
	Single active ingredients	2011	2012	2013	2014	Total	Total	Total	Total
1	AMOXICILLIN	201	255	253	261	227	4,505	1,197	0.266
2	AZITHROMYCIN DIHYDRATE	219	244	221	186	39	3,233	909	0.281
3	IBUPROFEN	113	141	141	149	152	1,696	696	0.410
4	ALBUTEROL SULFATE	79	115	145	98	119	1,875	556	0.297
5	LISINOPRIL	66	46	69	70	40	1,737	291	0.168
6	LEVOTHYROXINE SODIUM	38	63	46	48	50	2,393	245	0.102
7	CEPHALEXIN	46	28	50	51	27	553	202	0.365
8	PREDNISONE	32	42	46	48	23	438	191	0.436
9	NAPROXEN	31	26	40	34	44	499	175	0.351
10	ONDANSETRON HYDROCHLORIDE	19	32	45	46	29	258	171	0.663
11	OMEPRAZOLE	21	36	37	34	28	726	156	0.215
12	OXYCODONE HYDROCHLORIDE	24	35	26	33	22	255	140	0.549
13	ACETAMINOPHEN	44	37	38	8	9	308	136	0.442
14	CYCLOBENZAPRINE HYDROCHLORIDE	32	21	28	20	24	270	125	0.463
15	TRAMADOL HYDROCHLORIDE	12	27	19	32	33	293	123	0.420
16	METFORMIN HYDROCHLORIDE	38	32	11	16	25	802	122	0.152
17	PENICILLIN V POTASSIUM	25	19	23	36	18	328	121	0.369
18	METHYLPHENIDATE HYDROCHLORIDE	15	42	17	17	18	930	109	0.117
19	RANITIDINE HYDROCHLORIDE	20	39	14	21	14	343	108	0.315

20	SIMVASTATIN	20	25	20	22	20	1,022	107	0.105
21	SERTRALINE HYDROCHLORIDE	32	15	24	23	12	603	106	0.176
22	HYDROCHLOROTHIAZIDE	17	20	22	17	24	527	100	0.190
23	CIPROFLOXACIN HYDROCHLORIDE	15	21	24	16	24	305	100	0.328
24	PROMETHAZINE HYDROCHLORIDE	31	21	22	12	11	200	97	0.485
25	MONTELUKAST SODIUM	16	27	13	12	27	452	95	0.210
26	AMLODIPINE BESYLATE	5	13	33	22	18	722	91	0.126
27	CITALOPRAM HYDROBROMIDE	24	17	25	15	9	459	90	0.196
28	INSULIN HUMAN	18	15	20	20	16	309	89	0.288
29	ALPRAZOLAM	19	19	10	22	19	246	89	0.362
30	FLUTICASONE PROPIONATE	16	16	15	22	17	627	86	0.137

Table 5: Top 30 two-ingredient polypharmacy ranked by ER visits

		Number of ER					Occ	ER	#ER /#Occ
	Polypharmacy of two- ingredients	2011	2012	2013	2014	2015	Total	Total	Total
1	ACETAMINOPHEN-- HYDROCODONE BITARTRATE	121	98	99	180	130	1119	628	0.561
2	ACETAMINOPHEN-- CODEINE PHOSPHATE	71	68	83	48	47	632	317	0.502
3	AMOXICILLIN-- CLAVULANATE POTASSIUM	45	34	46	36	92	678	253	0.373
4	ACETAMINOPHEN-- OXYCODONE HYDROCHLORIDE	49	45	42	42	57	440	235	0.534
5	SULFAMETHOXAZOLE-- TRIMETHOPRIM	31	42	35	19	62	508	189	0.372
6	AMOXICILLIN-- IBUPROFEN	20	18	26	14	20	301	98	0.326
7	HYDROCHLOROTHIAZIDE-- LISINAPRIL	8	23	14	13	34	735	92	0.125
8	ALBUTEROL SULFATE-- PREDNISONE	10	14	18	16	9	75	67	0.893
9	AMOXICILLIN-- ALBUTEROL SULFATE	13	9	7	13	18	103	60	0.583
10	ALBUTEROL SULFATE-- FLUTICASONE PROPIONATE	8	17	12	7	12	190	56	0.295
11	CYCLOBENZAPRINE HYDROCHLORIDE-- IBUPROFEN	8	16	11	8	13	98	56	0.571

12	AZITHROMYCIN DIHYDRATE-- IBUPROFEN	8	13	8	15	3	122	47	0.385
13	IBUPROFEN--PREDNISONE	1	0	3	42	0	14	46	3.286
14	AMLODIPINE BESYLATE--LISINOPRIL	4	5	1	16	17	147	43	0.293
15	ETHINYL ESTRADIOL-- NORETHINDRONE ACETATE	2	13	7	2	12	311	36	0.116
16	AZITHROMYCIN DIHYDRATE-- PREDNISONE	5	7	12	5	7	63	36	0.571
17	ALBUTEROL SULFATE-- BUDESONIDE	4	13	6	7	3	100	33	0.330
18	CYCLOBENZAPRINE HYDROCHLORIDE--NAPROXEN	8	7	10	6	2	74	33	0.446
19	IBUPROFEN--TRAMADOL HYDROCHLORIDE	2	9	3	8	11	31	33	1.065
20	AMOXICILLIN--AZITHROMYCIN DIHYDRATE	15	2	5	6	4	63	32	0.508
21	SERTRALINE HYDROCHLORIDE-- TRAZODONE HYDROCHLORIDE	1	7	10	13	0	30	31	1.033
22	HYDROCODONE BITARTRATE-- HOMATROPINE METHYLBROMIDE	11	7	11	1	0	94	30	0.319
23	LISINOPRIL--SIMVASTATIN	10	6	3	5	5	222	29	0.131
24	ATENOLOL--CHLORTHALIDONE	8	8	3	9	1	145	29	0.200
25	ALBUTEROL SULFATE-- MONTELUKAST SODIUM	12	7	6	2	2	138	29	0.210
26	ALBUTEROL SULFATE-- PREDNISOLONE	7	9	4	7	2	52	29	0.558
27	ETONOGESTREL--ETHINYL ESTRADIOL	10	5	5	3	5	248	28	0.113
28	ALBUTEROL SULFATE-- BECLOMETHASONE DIPROPIONATE	4	9	5	3	7	104	28	0.269
29	AMLODIPINE BESYLATE-- HYDROCHLOROTHIAZIDE	1	6	6	8	5	113	26	0.230
30	AMOXICILLIN--PREDNISONE	4	1	5	15	1	49	26	0.530

Table 6: Top 30 three-ingredient polypharmacy ranked by ER visits.

		Number of ER					ER	#ER/ #Occ
	Polypharmacy of three-ingredients	2011	2012	2013	2014	2015	Total	Total
1	ACETAMINOPHEN--HYDROCODONE BITARTRATE--IBUPROFEN	8	23	15	57	34	137	0.840
2	ACETAMINOPHEN--IBUPROFEN-- OXYCODONE HYDROCHLORIDE	7	11	15	13	7	53	0.654
3	ACETAMINOPHEN-- CYCLOBENZAPRINE HYDROCHLORIDE--HYDROCODONE BITARTRATE	12	8	2	16	14	52	0.684
4	ALBUTEROL SULFATE--FLUTICASONE PROPIONATE--SALMETEROL XINAFOATE	10	8	10	13	6	47	0.285
5	ACETAMINOPHEN--HYDROCODONE BITARTRATE-- OXYCODONE HYDROCHLORIDE	6	8	14	10	2	40	0.727
6	ACETAMINOPHEN--CODEINE PHOSPHATE--IBUPROFEN	9	0	6	10	13	38	0.760
7	ACETAMINOPHEN--HYDROCODONE BITARTRATE--PROMETHAZINE HYDROCHLORIDE	4	4	9	14	3	34	1.478
8	AZITHROMYCIN DIHYDRATE-- ACETAMINOPHEN-- CODEINE PHOSPHATE	5	11	11	5	0	32	0.444
9	AZITHROMYCIN DIHYDRATE-- ACETAMINOPHEN-- HYDROCODONE BITARTRATE	5	12	4	9	1	31	0.660
10	ACETAMINOPHEN--BUTALBITAL-- CAFFEINE	3	5	5	9	8	30	0.476
11	HYDROCORTISONE--NEOMYCIN SULFATE-- POLYMYXIN B SULFATE	5	1	14	10	0	30	0.244
12	ACETAMINOPHEN--AZITHROMYCIN DIHYDRATE--CODEINE PHOSPHATE	3	8	10	7		28	0.571
13	ACETAMINOPHEN--CLINDAMYCIN PHOSPHATE-- HYDROCODONE BITARTRATE	0	2	4	11	11	28	0.875
14	ACETAMINOPHEN--HYDROCODONE BITARTRATE--PENICILLIN V POTASSIUM	6	2	5	6	6	25	0.455
15	AMLODIPINE BESYLATE-- HYDROCHLOROTHIAZIDE-- LOSARTAN POTASSIUM	0	11	4	2	8	25	0.357

16	AMOXICILLIN--ACETAMINOPHEN-- HYDROCODONE BITARTRATE	5	0	2	9	8	24	0.264
17	AMOXICILLIN--CLAVULANATE POTASSIUM--IBUPROFEN	4	1	3	12	4	24	0.828
18	ATENOLOL--CARISOPRODOL-- HYDROCHLOROTHIAZIDE			24			24	24.00
19	AMLODIPINE BESYLATE-- HYDROCHLOROTHIAZIDE--LISINOPRIL	4	1	9	8	1	23	0.228
20	ACETAMINOPHEN--AMOXICILLIN-- HYDROCODONE BITARTRATE	4	3	6	4	5	22	0.449
21	ACETAMINOPHEN--AZITHROMYCIN DIHYDRATE-- HYDROCODONE BITARTRATE	4	3	2	6	7	22	0.710
22	ACETAMINOPHEN--HYDROCODONE BITARTRATE--NAPROXEN	2	4	4	8	4	22	0.688
23	BROMPHENIRAMINE MALEATE-- DEXTROMETHORPHAN HYDROBROMIDE-- PSEUDOEPHEDRINE HYDROCHLORIDE	0	5	8	5	4	22	0.142
24	INSULIN GLARGINE--IBUPROFEN-- OMEPRazole		10	11			21	10.500
25	ACETAMINOPHEN--CEPHALEXIN-- HYDROCODONE BITARTRATE	7	6	1	4	0	18	0.375
26	ACETAMINOPHEN--CIPROFLOXACIN HYDROCHLORIDE--OXYCODONE HYDROCHLORIDE		7	2	5	4	18	2.571
27	ACETAMINOPHEN-- CYCLOBENZAPRINE HYDROCHLORIDE--OXYCODONE HYDROCHLORIDE	1	4	9	4	0	18	1.059
28	DIVALPROEX SODIUM-- LEVETIRACETAM -- OXCARBAZEPINE		6	12			18	3.600
29	ACETAMINOPHEN--AZITHROMYCIN DIHYDRATE-- OXYCODONE HYDROCHLORIDE	8	1	2	3	2	16	0.762
30	ALBUTEROL SULFATE--FLUTICASONE PROPRIONATE--MONTELUKAST SODIUM	1	1	11	0	3	16	0.347

Table 7: Single TC1-class polypharmacy in the dataset ranked by ER visits

		Number of ER					ER	
	Single TC1 Classes	2011	2012	2013	2014	2015	Total	#ER/ #occ
1	Central nervous system agents	1,278	1,375	1,141	1,538	1,460	6,792	0.396
2	Anti-infectives	825	790	980	807	651	4,053	0.3
3	Cardiovascular agents	379	361	692	404	409	2,245	0.206
4	Respiratory agents	307	340	442	254	304	1,647	0.257
5	Topical agents	213	210	511	248	310	1,492	0.226
6	Hormones/hormone modifiers	217	262	571	235	206	1,491	0.17
7	Metabolic agents	172	174	400	153	150	1,049	0.177
8	Psychotherapeutic agents	150	145	267	165	104	831	0.246
9	Gastrointestinal agents	101	160	183	152	118	714	0.279
10	Nutritional products	161	117	178	137	76	669	0.296
11	Coagulation modifiers	30	11	16	30	32	119	0.358
12	Antineoplastics	14	23	46	10	17	110	0.212
13	Miscellaneous agents	18	8	49	20	10	105	0.248
14	Genitourinary tract agents	3	3	16	2	3	27	0.157
15	Immunologic agents	2	5	4	10	2	23	0.168
16	Alternative medicines	1	0	3	14	2	20	0.351
17	Biologicals	0	0	0	0	0	0	0
	Grand Total	3,910	4,024	5,526	4,244	3,880	21,584	0.27

Table 8: Top 30 two TC1-class polypharmacy ranked by ER visits.

		Number of ER					Occ	ER	
	Polypharmacy of Two TC1-Classes	2011	2012	2013	2014	2015	Total	Total	#ER/#Occ
1	Anti-infectives--Central nervous system agents	397	417	208	436	398	3762	1856	0.493
2	Cardiovascular agents--Metabolic agents	234	225	609	227	201	8224	1496	0.182
3	Central nervous system agents--Psychotherapeutic agents	235	242	181	254	248	3072	1160	0.378
4	Central nervous system agents--Cardiovascular agents	138	150	91	184	123	1663	686	0.413
5	Anti-infectives--Respiratory agents	165	101	164	134	109	1893	673	0.356
6	Central nervous system agents--Hormones/hormone modifiers	101	106	100	144	119	1461	570	0.390
7	Central nervous system agents--Gastrointestinal agents	114	107	89	128	106	1091	544	0.499
8	Central nervous system agents--Respiratory agents	135	111	107	78	110	1275	541	0.424
9	Anti-infectives--Topical agents	88	94	129	84	84	1800	479	0.266
10	Cardiovascular agents--Central nervous system agents	66	99	74	114	94	1380	447	0.324
11	Central nervous system agents--Topical agents	59	86	66	73	125	1111	409	0.368
12	Central nervous system agents-- Metabolic agents	73	71	56	96	66	1196	362	0.303

13	Hormones/hormone modifiers--Respiratory agents	64	83	59	73	47	835	326	0.390
14	Respiratory agents--Topical agents	39	40	130	69	39	1197	317	0.265
15	Anti-infectives--Hormones/hormone modifiers	52	50	76	73	65	1075	316	0.294
16	Central nervous system agents--Nutritional products	78	62	63	45	55	602	303	0.503
17	Cardiovascular agents--Gastrointestinal agents	18	38	79	50	51	830	236	0.284
18	Anti-infectives--Cardiovascular agents	33	47	48	47	46	736	221	0.300
19	Cardiovascular agents--Hormones/hormone modifiers	25	40	59	42	48	1335	214	0.160
20	Cardiovascular agents--Psychotherapeutic agents	27	57	39	26	36	752	185	0.246
21	Cardiovascular agents--Nutritional products	28	39	38	40	34	501	179	0.357
22	Cardiovascular agents--Topical agents	34	15	50	37	31	651	167	0.257
23	Hormones/hormone modifiers--Topical agents	19	24	49	30	16	631	138	0.219
24	Cardiovascular agents--Respiratory agents	26	26	32	25	22	504	131	0.260
25	Anti-infectives--Metabolic agents	17	20	33	23	24	347	117	0.337
26	Anti-infectives--Nutritional products	25	27	18	30	14	277	114	0.412
27	Anti-infectives--Gastrointestinal agents	10	24	13	28	37	322	112	0.348

28	Hormones/hormone modifiers-- Psychotherapeutic agents	18	24	39	14	13	577	108	0.187
29	Hormones/hormone modifiers--Nutritional products	15	16	37	4	25	184	97	0.527
30	Gastrointestinal agents--Nutritional products	13	8	28	28	18	144	95	0.660

Table 9: Top 30 three TC1-class polypharmacy ranked by ER visits.

		Number of ER					Occ	ER	
		2011	2012	2013	2014	2015	Total	Total	
	Polypharmacy of Three TC1-Classes								#ER/#Occ
1	Cardiovascular agents--Central nervous system agents--Metabolic agents	52	83	108	84	62	1376	389	0.283
2	Central nervous system agents--Cardiovascular agents--Metabolic agents	57	82	80	109	53	1157	381	0.329
3	Central nervous system agents--Cardiovascular agents--Psychotherapeutic agents	48	55	41	70	93	648	307	0.474
4	Anti-infectives--Central nervous system agents--Psychotherapeutic agents	110	54	24	76	33	409	297	0.726
5	Anti-infectives--Central nervous system agents--Topical agents	49	42	50	54	62	489	257	0.526
6	Anti-infectives--Central nervous system agents--Respiratory agents	47	54	52	50	50	540	253	0.469
7	Anti-infectives--Hormones/hormone modifiers--Respiratory agents	34	23	53	60	47	1038	217	0.209
8	Cardiovascular agents--Gastrointestinal agents--Metabolic agents	48	50	21	52	46	473	217	0.459
9	Anti-infectives--Central nervous system agents--Gastrointestinal agents	35	36	49	37	57	282	214	0.759
10	Anti-infectives--Central nervous system agents--Hormones/hormone modifiers	59	29	44	38	40	439	210	0.478

11	Cardiovascular agents-- Coagulation modifiers-- Metabolic agents	31	50	41	43	32	525	197	0.375
12	Cardiovascular agents-- Hormones/hormone modifiers-- Metabolic agents	44	41	40	37	32	1159	194	0.167
13	Central nervous system agents-- Gastrointestinal agents-- Psychotherapeutic agents	30	32	21	74	31	307	188	0.612
14	Anti-infectives--Central nervous system agents--Cardiovascular agents	44	38	21	34	43	283	180	0.636
15	Central nervous system agents-- Hormones/hormone modifiers-- Psychotherapeutic agents	30	29	27	29	51	473	166	0.351
16	Cardiovascular agents--Central nervous system agents-- Psychotherapeutic agents	27	32	29	26	34	386	148	0.383
17	Central nervous system agents-- Psychotherapeutic agents-- Respiratory agents	25	12	24	45	41	271	147	0.542
18	Coagulation modifiers-- Cardiovascular agents-- Metabolic agents	24	36	43	15	25	375	143	0.381
19	Cardiovascular agents--Central nervous system agents-- Gastrointestinal agents	25	36	35	32	10	228	138	0.605
20	Anti-infectives--Respiratory agents--Topical agents	28	20	24	27	31	445	130	0.292
21	Anti-infectives--Cardiovascular agents-- Metabolic agents	22	20	39	22	25	490	128	0.261
22	Central nervous system agents-- Cardiovascular agents-- Gastrointestinal agents	36	15	14	32	24	305	121	0.397
23	Cardiovascular agents-- Metabolic agents--Nutritional products	15	19	29	30	24	622	117	0.188
24	Central nervous system agents-- Metabolic agents -- Psychotherapeutic agents	12	15	32	36	20	319	115	0.361
25	Cardiovascular agents-- Metabolic agents --Topical agents	13	25	37	22	16	652	113	0.173
26	Cardiovascular agents-- Metabolic agents -- Psychotherapeutic agents	9	19	36	12	27	567	103	0.182
27	Central nervous system agents-- Respiratory agents--Topical agents	17	24	17	13	32	310	103	0.332
28	Anti-infectives--Central nervous system agents-- Metabolic agents	19	29	6	18	19	208	91	0.438

29	Central nervous system agents-- Gastrointestinal agents- Metabolic agents	16	16	31	16	11	204	90	0.441
30	Anti-infectives-- Cardiovascular agents- Central nervous system agents	20	9	4	34	18	158	85	0.538

Table 10: Top 30 single TC1S1-class in the dataset ranked by ER visits.

		Number of ER					ER	
	Single TC1S1-Classes	2011	2012	2013	2014	2015	Total	#ER/#Occ
1	ANALGESICS	752	802	781	877	761	3,973	0.466
2	PENICILLINS	287	317	335	336	316	1,591	0.284
3	MACROLIDE_DERIVATIVES	230	254	223	186	39	932	0.278
4	BRONCHODILATORS	127	152	173	125	146	723	0.269
5	DERMATOLOGICAL_AGENTS	123	129	139	131	185	707	0.213
6	ANTIDEPRESSANTS	117	121	131	118	88	575	0.206
7	SEX_HORMONES	119	131	108	100	101	559	0.113
8	ANTICONVULSANTS	85	115	131	89	85	505	0.395
9	ANTIEMETIC/ANTIVERTIGO_AGENTS	73	90	91	86	80	420	0.580
10	ANTIDIABETIC_AGENTS	103	92	70	70	71	406	0.195
11	IRON_PRODUCTS	102	81	95	85	31	394	0.389
12	CNS_STIMULANTS	51	94	80	75	87	387	0.131
13	ANGIOTENSIN_CONVERTING _ENZYME_INHIBITORS	76	49	87	75	42	329	0.164
14	PROTON_PUMP_INHIBITORS	56	74	73	61	51	315	0.220
15	ADRENAL_CORTICAL_STEROIDS	52	58	77	73	42	302	0.387
16	CEPHALOSPORINS	67	45	66	70	42	290	0.333
17	OPHTHALMIC_PREPARATIONS	34	52	85	55	64	290	0.167
18	ANTIHYPERLIPIDEMIC_AGENTS	50	58	54	58	62	282	0.096
19	THYROID_HORMONES	40	65	48	50	55	258	0.101
20	ANTIHYPERTENSIVE_COMBINATIONS	53	44	40	56	49	242	0.126
21	MISCELLANEOUS_ANTIBIOTICS	33	45	44	21	60	203	0.373
22	BETA-ADRENERGIC_BLOCKING_AGENTS	40	47	37	35	37	196	0.178
23	MUSCLE_RELAXANTS	39	26	36	35	30	166	0.376
24	ANTIHISTAMINES	29	37	28	36	34	164	0.178
25	DIURETICS	31	32	34	31	36	164	0.229
26	ANTIVIRAL_AGENTS	39	23	28	34	36	160	0.216
27	ANXIOLYTICSEDATIVESAND_HYPNOTICS	30	33	23	45	29	160	0.251
28	(H2_ANTAGONISTS)	27	51	24	28	20	150	0.351
29	UPPER_RESPIRATORY_COMBINATIONS	39	31	44	20	16	150	0.182
30	QUINOLONES	27	26	40	28	20	141	0.359

Table 11: Top 30 two TC1S1-class polypharmacy ranked by ER visits.

		Number of ER					Occ	ER	
	Polypharmacy of Two TC1S1-Classes	2011	2012	2013	2014	2015	Total	Total	#ER/#Occ
1	ANALGESICS--MUSCLE_RELAXANTS	94	116	105	117	93	921	525	0.57
2	ANALGESICS--PENICILLINS	88	81	139	106	105	1,169	519	0.44
3	ANALGESICS--MACROLIDE_DERIVATIVES	70	95	74	77	19	609	335	0.55
4	ANALGESICS--ANTIEMETIC/ANTIVERTIGO_AGENTS	26	23	50	58	51	176	208	1.18
5	ADRENAL_CORTICAL_STEROIDS--BRONCHODILATORS	30	58	43	39	22	319	192	0.60
6	ANALGESICS--ANTICONVULSANTS	19	37	17	37	52	281	162	0.58
7	ANALGESICS--DERMATOLOGICAL_AGENTS	25	33	24	14	64	322	160	0.50
8	ANALGESICS--CEPHALOSPORINS	36	17	18	38	14	223	123	0.55
9	ANALGESICS--PROTON_PUMP_INHIBITORS	26	30	23	14	21	260	114	0.44
10	ANALGESICS--IRON_PRODUCTS	24	20	33	22	8	157	107	0.68
11	ANALGESICS--MISCELLANEOUS_ANTIBIOTICS	20	13	21	6	42	114	102	0.89
12	ANALGESICS--SEX_HORMONES	22	20	13	26	20	278	101	0.36
13	BRONCHODILATORS--PENICILLINS	21	19	14	23	23	210	100	0.48
14	BRONCHODILATORS--RESPIRATORY_INHALANT_PRODUCTS	17	29	18	11	18	308	93	0.30
15	ANALGESICS--BRONCHODILATORS	32	8	13	15	22	149	90	0.60
16	ANALGESICS--ANTIDEPRESSANTS	12	16	30	20	10	200	88	0.44
17	ANTIEMETIC/ANTIVERTIGO_AGENTS--ANALGESICS	8	6	32	9	33	89	88	0.99
18	ANALGESICS--QUINOLONES	13	16	22	8	23	96	82	0.85
19	MACROLIDE_DERIVATIVES--PENICILLINS	32	4	19	16	9	148	80	0.54
20	ADRENAL_CORTICAL_STEROIDS--ANALGESICS	6	9	9	50	5	80	79	0.99
21	ANTIDEPRESSANTS--ANTICONVULSANTS	15	20	7	10	24	192	76	0.40
22	ANALGESICS--LINCOMYCIN_DERIVATIVES	7	14	11	28	15	100	75	0.75
23	ANTICONVULSANTS--ANALGESICS	10	15	10	11	27	165	73	0.44
24	ANALGESICS--LAXATIVES	9	7	21	23	10	142	70	0.49
25	ANALGESICS--ANTIHYPERTENSIVE_COMBINATIONS	11	12	13	13	18	120	67	0.56
26	ANALGESICS--DIURETICS	21	23	6	5	11	101	66	0.65
27	ANALGESICS--BETA_ADRENERGIC_BLOCKING_AGENTS	18	17	18	7	5	138	65	0.47
28	BRONCHODILATORS--LEUKOTRIENE_MODIFIERS	29	10	12	6	5	263	62	0.24
29	BRONCHODILATORS--MACROLIDE_DERIVATIVES	20	13	5	17	7	175	62	0.35
30	ANALGESICS--ADRENAL_CORTICAL_STEROIDS	10	17	9	8	18	99	62	0.63

Table 12: Top 30 three TC1S1-class polypharmacy ranked by ER visits.

	Polypharmacy of Three TC1S1-Classes	Number of ER					Occ	ER	#ER /#Occ
		2011	2012	2013	2014	2015	Total	Total	
1	ADRENAL_CORTICAL_STEROIDS--BRONCHODILATORS--MACROLIDE_DERIVATIVES	11	13	7	9	12	77	52	0.68
2	ANALGESICS--ANTICONVULSANTS--MUSCLE_RELAXANTS	12	8	5	9	11	66	45	0.68
3	ANALGESICS--ANTIDEPRESSANTS--ANXIOLYTICSEDATIVESAND_HYPNOTICS	27	5	4	7	0	23	43	1.87
4	ADRENAL_CORTICAL_STEROIDS--BRONCHODILATORS--PENICILLINS	7	6	15	7	2	56	37	0.66
5	ANALGESICS--PENICILLINS--UPPER_RESPIRATORY_COMBINATIONS	7	9	11	3	0	66	30	0.45
6	ANTIDIABETIC_AGENTS--ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS--ANTIHYPERTENSIVE_COMBINATIONS	5	10	7	4	3	185	29	0.16
7	ANALGESICS--ANTICONVULSANTS--ANTIDEPRESSANTS	7	3	7	1	10	33	28	0.85
8	ANTIDIABETIC_AGENTS--ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS--BETA--ADRENERGIC_BLOCKING_AGENTS	5	8	2	10	1	43	26	0.60
9	BRONCHODILATORS--LEUKOTRIENE_MODIFIERS--RESPIRATORY_INHALANT_PRODUCTS	6	1	15	3	1	62	26	0.42
10	ANALGESICS--IRON_PRODUCTS--LAXATIVES	6	4	8	7	0	31	25	0.81
11	ANALGESICS--ANTIDEPRESSANTS--MUSCLE_RELAXANTS	2	7	4	5	6	46	24	0.52
12	BETA--ADRENERGIC_BLOCKING_AGENTS--DIURETICS--MUSCLE_RELAXANTS			24	0		2	24	12.00
13	ANALGESICS--ANTIEMETIC/ANTIVERTIGO_AGENTS--MUSCLE_RELAXANTS	9		2	9	3	15	23	1.53
14	ANALGESICS--MACROLIDE_DERIVATIVES--PENICILLINS	8	4	9	1	1	30	23	0.77
15	ANALGESICS--MUSCLE_RELAXANTS--PROTON_PUMP_INHIBITORS	5	9	2	1	6	41	23	0.56
16	ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS--BETA--ADRENERGIC_BLOCKING_AGENTS--DIURETICS	1	4	3	9	6	86	23	0.27
17	ANALGESICS--ANTIDEPRESSANTS--ANTICONVULSANTS	1	7	6	3	5	39	22	0.56
18	ANALGESICS--MUSCLE_RELAXANTS--PENICILLINS	1	3	8	9	1	21	22	1.05
19	ANTIDIABETIC_AGENTS--ANALGESICS--PROTON_PUMP_INHIBITORS	0	10	11	0	0	9	21	2.33
20	ANTIHYPERTENSIVE_COMBINATIONS--BETA--ADRENERGIC_BLOCKING_AGENTS--CALCIUM_CHANNEL_BLOCKING_AGENTS	0	4	15	0	2	44	21	0.48
21	BETA_ADRENERGIC_BLOCKING_AGENTS--CALCIUM_CHANNEL_BLOCKING_AGENTS--DIURETICS	2	3	0	11	5	40	21	0.53
22	ADRENAL_CORTICAL_STEROIDS--BRONCHODILATORS--RESPIRATORY_INHALANT_PRODUCTS	3	8	2	2	5	29	20	0.69
23	ANALGESICS--ANTIEMETIC/ANTIVERTIGO_AGENTS--PENICILLINS	1	8	3	4	4	24	20	0.83
24	ANALGESICS--OTIC_PREPARATIONS--PENICILLINS	7	1	1	5	6	21	20	0.95
25	ANALGESICS--ANTIEMETIC/ANTIVERTIGO_AGENTS--MACROLIDE_DERIVATIVES	1	4	9	3	2	17	19	1.12

26	ANALGESICS--BRONCHODILATORS-- RESPIRATORY_INHALANT_PRODUCTS	13	4	1	1	0	22	19	0.86
27	ANALGESICS--CEPHALOSPORINS-- MISCELLANEOUS_ANTIBIOTICS	3	2	1	7	6	16	19	1.19
28	ANTICOAGULANTS--ANTIARRHYTHMIC_AGENTS-- BETA_ADRENERGIC_BLOCKING_AGENTS		2	8	2	7	15	19	1.27
29	ADRENAL_CORTICAL_STEROIDS--BRONCHODILATORS-- QUINOLONES	0	7	1	5	4	15	17	1.13
30	ANALGESICS--IRON_PRODUCTS--VITAMINS		7	4	1	5	16	17	1.06

C Richness of three-elements polypharmacy

Table 13: Top 30 drug-triples and their individual and co-occurrences probability, and occurrence richness ranked by ER total.

	Drug triples	Occ	part1- occ	part2- occ	part3- occ	p(three- occ)	p(part1- occ)	p(part2- occ)	p(part3- occ)	Occ- richness
1	CYCLOBENZAPR-- HYDROCO/APAP-- IBUPROFEN	29	260	1238	1675	0.00113	0.0038	0.0182	0.0247	651.95
2	ATENOLOL-- CARISOPRODOL-- HYDROCHLOROT	1	447	37	463	0.00004	0.0066	0.0005	0.0068	1582.84
3	IBUPROFEN-- LANTUS-- OMEPRAZOLE	2	1675	75	721	0.00008	0.0247	0.0011	0.0106	267.64
4	AMLODIPINE-- METOPROLOL-- VALSART/HCTZ	5	684	184	34	0.00019	0.0101	0.0027	0.0005	14162.66
5	DIVALPROEX-- LEVETIRACETA-- OXCARBAZEPIN	3	46	104	72	0.00012	0.0007	0.0015	0.0011	105566.29
6	CLINDAMYCIN-- CYCLOBENZAPR-- OXYCODONE	1	260	260	211	0.00004	0.0038	0.0038	0.0031	849.76
7	GLIPIZIDE-- LISINOPRIL-- METFORMIN	33	38	1737	780	0.00128	0.0006	0.0256	0.0115	7768.97
8	ALBUTEROL-- AMOXICILLIN-- PREDNISONE	5	785	4471	436	0.00019	0.0116	0.0659	0.0064	39.60
9	AMOXICILLIN-- HYDROCO/APAP-- IBUPROFEN	20	4471	1238	1675	0.00078	0.0659	0.0182	0.0247	26.15
10	APAP/CODEINE-- AZITHROMYCIN-- IBUPROFEN	6	614	3180	1675	0.00023	0.0090	0.0469	0.0247	22.24
11	CEPHALEXIN-- HYDROCO/APAP-- IBUPROFEN	5	538	1238	1675	0.00019	0.0079	0.0182	0.0247	54.32
12	MIRTAZAPINE-- PRAVASTATIN-- TERAZOSIN	3	28	257	22	0.00012	0.0004	0.0038	0.0003	229686.31
13	LISINOPRIL-- PERCOCET-- SIMVASTATIN	1	1737	62	1014	0.00004	0.0256	0.0009	0.0149	110.99
14	AMOXICILLIN-- APAP/CODEINE-- IBUPROFEN	9	4471	614	1675	0.00035	0.0659	0.0090	0.0247	23.72

15	FEXOFENADINE-- LEVETIRACETA-- VITAMIN D	3	23	104	217	0.00012	0.0003	0.0015	0.0032	70053.21
16	AMOX/K CLAV-- HYDROMORPHON-- -NEXIUM	1	485	14	186	0.00004	0.0071	0.0002	0.0027	9597.21
17	ALBUTEROL-- QVAR-- TRAMADOL_HCL	1	785	61	41	0.00004	0.0116	0.0009	0.0006	6173.68
18	ALBUTEROL-- AZITHROMYCIN-- PREDNISOLONE	11	785	3180	150	0.00043	0.0116	0.0469	0.0022	356.07
19	AZITHROMYCIN-- PREDNISONE-- VENTOLIN HFA	7	3180	436	318	0.00027	0.0469	0.0064	0.0047	192.44
20	HYDROCO/APAP-- IBUPROFEN-- OXYCOD/APAP	5	1238	1675	324	0.00019	0.0182	0.0247	0.0048	90.20
21	AMLODIPINE-- HYDROCO/APAP-- LISINOPRIL	5	684	1238	1737	0.00019	0.0101	0.0182	0.0256	41.20
22	ALBUTEROL-- FLOVENT DISK-- PREDNISONE	4	785	31	436	0.00016	0.0116	0.0005	0.0064	4569.51
23	CARISOPRODOL-- IBUPROFEN-- PROMETHAZINE	2	37	1675	187	0.00008	0.0005	0.0247	0.0028	2091.70
24	ALPRAZOLAM-- FOLIC_ACID-- HYDROCO/APAP	2	227	12	1238	0.00008	0.0033	0.0002	0.0182	7188.36
25	ALBUTEROL-- AMOX/K CLAV-- PREDNISONE	2	785	485	436	0.00008	0.0116	0.0071	0.0064	146.04
26	ACETAMINOPHEN TAB 500 MG-- ATORVASTATIN-- PROPRAN/HCTZ	2	26	556	126	0.00008	0.0004	0.0082	0.0019	13308.80
27	HYDROXYZ HCL-- RANITIDINE-- TRAZODONE	1	54	327	80	0.00004	0.0008	0.0048	0.0012	8580.18
28	HYDROCOD/HOM-- -LISINOPRIL-- QUETIAPINE	1	57	1737	29	0.00004	0.0008	0.0256	0.0004	4221.39
29	ESCITALOPRAM-- ONDANSETRON-- OXYCODONE	1	197	254	211	0.00004	0.0029	0.0037	0.0031	1148.01
30	DICLOFENAC-- HYDROCHLOROT-- RANITIDINE	1	116	463	327	0.00004	0.0017	0.0068	0.0048	690.15

Table 14: Individual and joint probability of occurrence for the top 30 two- drug polypharmacy (sorted by ER total) with richness of ER.

	Drug triples	ER	part1- EROcc	part2- EROcc	part3- EROcc	p(part1- ERocc)	p(part2- ERocc)	p(part 3- ERocc)	p(three- case-ER)	ER-richness
1	CYCLOBENZAPR-- HYDROCO/APAP-- IBUPROFEN	27	122	698	691	0.0076	0.0436	0.0431	0.0033	229.43
2	ATENOLOL-- CARISOPRODOL-- HYDROCHLOROT	24	66	3	85	0.0041	0.0002	0.0053	0.0029	713024.60
3	IBUPROFEN-- LANTUS-- OMEPRAZOLE	21	691	18	154	0.0431	0.0011	0.0096	0.0026	5481.83
4	AMLODIPINE-- METOPROLOL-- VALSART/HCTZ	12	81	36	6	0.0051	0.0022	0.0004	0.0015	342941.36
5	DIVALPROEX-- LEVETIRACETA-- OXCARBAZEPIN	12	29	54	11	0.0018	0.0034	0.0007	0.0015	348316.62
6	CLINDAMYCIN-- CYCLOBENZAPR-- OXYCODONE	12	77	122	115	0.0048	0.0076	0.0072	0.0015	5554.06
7	GLIPIZIDE-- LISINOPRIL-- METFORMIN	11	3	291	114	0.0002	0.0182	0.0071	0.0013	55265.10
8	ALBUTEROL-- AMOXICILLIN-- PREDNISONE	11	275	1190	190	0.0172	0.0743	0.0119	0.0013	88.46
9	AMOXICILLIN-- HYDROCO/APAP-- IBUPROFEN	10	1190	698	691	0.0743	0.0436	0.0431	0.0012	8.71
10	APAP/CODEINE-- AZITHROMYCIN-- IBUPROFEN	10	304	891	691	0.0190	0.0556	0.0431	0.0012	26.71
11	CEPHALEXIN-- HYDROCO/APAP-- IBUPROFEN	10	196	698	691	0.0122	0.0436	0.0431	0.0012	52.89
12	MIRTAZAPINE-- PRAVASTATIN-- TERAZOSIN	10	3	30	4	0.0002	0.0019	0.0002	0.0012	13889125. 08
13	LISINOPRIL-- PERCOCET-- SIMVASTATIN	10	291	21	106	0.0182	0.0013	0.0066	0.0012	7718.97
14	AMOXICILLIN-- APAP/CODEINE-- IBUPROFEN	9	1190	304	691	0.0743	0.0190	0.0431	0.0011	18.00
15	FEXOFENADINE-- LEVETIRACETA-- VITAMIN D	9	3	54	26	0.0002	0.0034	0.0016	0.0011	1068394.2 4
16	AMOX/K CLAV-- HYDROMORPHON --NEXIUM	9	187	8	29	0.0117	0.0005	0.0018	0.0011	103726.64
17	ALBUTEROL-- QVAR-- TRAMADOL_HCL	9	275	17	12	0.0172	0.0011	0.0007	0.0011	80215.27
18	ALBUTEROL-- AZITHROMYCIN-- PREDNISOLONE	8	275	891	54	0.0172	0.0556	0.0034	0.0010	302.32
19	AZITHROMYCIN-- PREDNISONE-- VENTOLIN HFA	8	891	190	75	0.0556	0.0119	0.0047	0.0010	315.05

20	HYDROCO/APAP-- IBUPROFEN-- OXYCOD/APAP	8	698	691	175	0.0436	0.0431	0.0109	0.0010	47.39
21	AMLODIPINE-- HYDROCO/APAP-- LISINOPRIL	8	81	698	291	0.0051	0.0436	0.0182	0.0010	243.13
22	ALBUTEROL-- FLOVENT DISK-- PREDNISONE	8	275	15	190	0.0172	0.0009	0.0119	0.0010	5103.76
23	CARISOPRODOL-- IBUPROFEN-- PROMETHAZINE	8	3	691	85	0.0002	0.0431	0.0053	0.0010	22701.22
24	ALPRAZOLAM-- FOLIC_ACID-- HYDROCO/APAP	8	81	3	698	0.0051	0.0002	0.0436	0.0010	23583.36
25	ALBUTEROL-- AMOX/K CLAV-- PREDNISONE	8	275	187	190	0.0172	0.0117	0.0119	0.0010	409.39
26	ACETAMINOPHEN TAB 500 MG-- ATORVASTATIN-- PROPRAN/HCTZ	8	13	45	20	0.0008	0.0028	0.0012	0.0010	341886.16
27	HYDROXYZ HCL-- RANITIDINE-- TRAZODONE	8	10	99	13	0.0006	0.0062	0.0008	0.0010	310805.60
28	HYDROCOD/HOM-- -LISINOPRIL-- QUETIAPINE	8	16	291	11	0.0010	0.0182	0.0007	0.0010	78101.92
29	ESCITALOPRAM-- ONDANSETRON-- OXYCODONE	8	37	167	115	0.0023	0.0104	0.0072	0.0010	5629.26
30	DICLOFENAC-- HYDROCHLOROT-- RANITIDINE	8	25	85	99	0.0016	0.0053	0.0062	0.0010	19013.99

Figure 1: Relationship between drug triples and occurrence and ER richness. Logarithms are in base 10.

Table 15: Top 30 active ingredient-triples and their individual and co-occurrences probability, and occurrence richness ranked by ER total.

	Active ingredient triples	Occ	part1-occ	part2-occ	part3-occ	p(three-occ)	p(part1-occ)	p(part2-occ)	p(part3-occ)	Occ-richness
1	ACETAMINOPHEN--HYDROCODONE BITARTRATE--IBUPROFEN	163	308	47	1696	0.0061	0.0052	0.0008	0.0287	50648.74
2	ACETAMINOPHEN--IBUPROFEN--OXYCODONE HYDROCHLORIDE	81	308	1696	255	0.0030	0.0052	0.0287	0.0043	4638.99
3	ACETAMINOPHEN--CYCLOBENZAPRINE HYDROCHLORIDE--HYDROCODONE BITARTRATE	76	308	270	47	0.0028	0.0052	0.0046	0.0008	148339.47
4	ALBUTEROL SULFATE--FLUTICASONE PROPIONATE--SALMETEROL XINAFOATE	165	1875	627	1	0.0061	0.0318	0.0106	0.0000	1070706.91

5	ACETAMINOPHEN-- HYDROCODONE BITARTRATE--OXYCODONE HYDROCHLORIDE	55	308	47	255	0.0020	0.0052	0.0008	0.0043	113665.69
6	ACETAMINOPHEN-- CODEINE PHOSPHATE-- IBUPROFEN	50	308	-	1696	0.0019	0.0052	-	0.0287	-
7	ACETAMINOPHEN-- HYDROCODONE BITARTRATE-- PROMETHAZINE HYDROCHLORIDE	23	308	47	200	0.0009	0.0052	0.0008	0.0034	60604.48
8	AZITHROMYCIN DIHYDRATE-- ACETAMINOPHEN-- CODEINE PHOSPHATE	72	3233	308	-	0.0027	0.0548	0.0052	-	-
9	AZITHROMYCIN DIHYDRATE-- ACETAMINOPHEN-- HYDROCODONE BITARTRATE	47	3233	308	47	0.0017	0.0548	0.0052	0.0008	7661.24
10	ACETAMINOPHEN-- BUTALBITAL--CAFFEINE	63	308	-	-	0.0023	0.0052	-	-	-
11	HYDROCORTISONE-- NEOMYCIN SULFATE-- POLYMYXIN B SULFATE	123	286	4	-	0.0046	0.0048	0.0001	-	-
12	ACETAMINOPHEN-- AZITHROMYCIN DIHYDRATE--CODEINE PHOSPHATE	49	308	3233	-	0.0018	0.0052	0.0548	-	-
13	ACETAMINOPHEN-- CLINDAMYCIN PHOSPHATE-- HYDROCODONE BITARTRATE	32	308	263	47	0.0012	0.0052	0.0045	0.0008	64121.12
14	ACETAMINOPHEN-- HYDROCODONE BITARTRATE--PENICILLIN V POTASSIUM	55	308	47	328	0.0020	0.0052	0.0008	0.0056	88368.15
15	AMLODIPINE BESYLATE-- HYDROCHLOROTHIAZIDE-- LOSARTAN POTASSIUM	70	722	527	294	0.0026	0.0122	0.0089	0.0050	4773.74
16	AMOXICILLIN-- ACETAMINOPHEN-- HYDROCODONE BITARTRATE	91	4505	308	47	0.0034	0.0764	0.0052	0.0008	10645.19
17	AMOXICILLIN-- CLAVULANATE POTASSIUM--IBUPROFEN	29	4505	-	1696	0.0011	0.0764	-	0.0287	-
18	ATENOLOL-- CARISOPRODOL-- HYDROCHLOROTHIAZIDE	1	447	37	527	0.0000	0.0076	0.0006	0.0089	875.26
19	AMLODIPINE BESYLATE-- HYDROCHLOROTHIAZIDE-- LISINAPRIL	101	722	527	1737	0.0038	0.0122	0.0089	0.0294	1165.81

20	ACETAMINOPHEN-- AMOXICILLIN-- HYDROCODONE BITARTRATE	49	308	4505	47	0.0018	0.0052	0.0764	0.0008	5732.03
21	ACETAMINOPHEN-- AZITHROMYCIN DIHYDRATE-- HYDROCODONE BITARTRATE	31	308	3233	47	0.0012	0.0052	0.0548	0.0008	5053.16
22	ACETAMINOPHEN-- HYDROCODONE BITARTRATE--NAPROXEN	32	308	47	499	0.0012	0.0052	0.0008	0.0085	33795.30
23	BROMPHENIRAMINE MALEATE-- DEXTROMETHORPHAN HYDROBROMIDE-- PSEUDOEPHEDRINE HYDROCHLORIDE	155	-	5	20	0.0058	-	0.0001	0.0003	-
24	INSULIN GLARGINE-- IBUPROFEN--OMEPRazole	2	79	1696	726	0.0001	0.0013	0.0287	0.0123	156.85
25	ACETAMINOPHEN-- CEPHALEXIN-- HYDROCODONE BITARTRATE	48	308	553	47	0.0018	0.0052	0.0094	0.0008	45742.83
26	ACETAMINOPHEN-- CIPROFLOXACIN HYDROCHLORIDE-- OXYCODONE HYDROCHLORIDE	7	308	305	255	0.0003	0.0052	0.0052	0.0043	2229.27
27	ACETAMINOPHEN-- CYCLOBENZAPRINE HYDROCHLORIDE-- OXYCODONE HYDROCHLORIDE	17	308	270	255	0.0006	0.0052	0.0046	0.0043	6115.75
28	DIVALPROEX SODIUM-- LEVETIRACETAM-- OXCARBAZEPINE	5	49	112	82	0.0002	0.0008	0.0019	0.0014	84761.28
29	ACETAMINOPHEN-- AZITHROMYCIN DIHYDRATE--OXYCODONE HYDROCHLORIDE	21	308	3233	255	0.0008	0.0052	0.0548	0.0043	630.93
30	ALBUTEROL SULFATE-- FLUTICASONE PROPIONATE-- MONTELUKAST SODIUM	46	1875	627	452	0.0017	0.0318	0.0106	0.0077	660.40

Table 16: Individual and joint probability of occurrence for the top 30 two- active ingredients polypharmacy (sorted by ER total) with richness of ER.

	Active ingredient triples	ER	part1- EROcc	part2- EROcc	part3- EROcc	p(part1- EROcc)	p(part2- EROcc)	p(part3- EROcc)	p(three- case-ER)	ER- richness
1	ACETAMINOPHEN-- HYDROCODONE BITARTRATE--IBUPROFEN	137	136	13	696	0.0101	0.0010	0.0517	0.0159	31661.23
2	ACETAMINOPHEN-- IBUPROFEN--OXYCODONE HYDROCHLORIDE	53	136	696	140	0.0101	0.0517	0.0104	0.0062	1137.36

3	ACETAMINOPHEN-- CYCLOBENZAPRINE HYDROCHLORIDE-- HYDROCODONE BITARTRATE	52	136	125	13	0.0101	0.0093	0.0010	0.0060	66912.90
4	ALBUTEROL SULFATE-- FLUTICASONE PROPIONATE--SALMETEROL XINAFOATE	47	556	86	2	0.0413	0.0064	0.0001	0.0055	139763.38
5	ACETAMINOPHEN-- HYDROCODONE BITARTRATE--OXYCODONE HYDROCHLORIDE	40	136	13	140	0.0101	0.0010	0.0104	0.0047	45956.66
6	ACETAMINOPHEN-- CODEINE PHOSPHATE-- IBUPROFEN	38	136	-	696	0.0101	-	0.0517	0.0044	-
7	ACETAMINOPHEN-- HYDROCODONE BITARTRATE-- PROMETHAZINE HYDROCHLORIDE	34	136	13	97	0.0101	0.0010	0.0072	0.0040	56379.82
8	AZITHROMYCIN DIHYDRATE-- ACETAMINOPHEN-- CODEINE PHOSPHATE	32	909	136	-	0.0675	0.0101	-	0.0037	-
9	AZITHROMYCIN DIHYDRATE-- ACETAMINOPHEN-- HYDROCODONE BITARTRATE	31	909	136	13	0.0675	0.0101	0.0010	0.0036	5485.48
10	ACETAMINOPHEN-- BUTALBITAL--CAFFEINE	30	136	-	-	0.0101	-	-	0.0035	-
11	HYDROCORTISONE-- NEOMYCIN SULFATE-- POLYMYXIN B SULFATE	30	72	0	-	0.0053	0.0000	-	0.0035	-
12	ACETAMINOPHEN-- AZITHROMYCIN DIHYDRATE--CODEINE PHOSPHATE	28	136	909	-	0.0101	0.0675	-	0.0033	-
13	ACETAMINOPHEN-- CLINDAMYCIN PHOSPHATE- -HYDROCODONE BITARTRATE	28	136	77	13	0.0101	0.0057	0.0010	0.0033	58490.30
14	ACETAMINOPHEN-- HYDROCODONE BITARTRATE--PENICILLIN V POTASSIUM	25	136	13	121	0.0101	0.0010	0.0090	0.0029	33233.12
15	AMLODIPINE BESYLATE-- HYDROCHLOROTHIAZIDE-- LOSARTAN POTASSIUM	25	91	100	42	0.0068	0.0074	0.0031	0.0029	18601.51
16	AMOXICILLIN-- ACETAMINOPHEN-- HYDROCODONE BITARTRATE	24	1197	136	13	0.0889	0.0101	0.0010	0.0028	3225.03
17	AMOXICILLIN-- CLAVULANATE POTASSIUM- -IBUPROFEN	24	1197	-	696	0.0889	-	0.0517	0.0028	-
18	ATENOLOL-- CARISOPRODOL-- HYDROCHLOROTHIAZIDE	24	66	3	100	0.0049	0.0002	0.0074	0.0028	344702.82
19	AMLODIPINE BESYLATE-- HYDROCHLOROTHIAZIDE-- LISINAPRIL	23	91	100	291	0.0068	0.0074	0.0216	0.0027	2469.97

20	ACETAMINOPHEN-- AMOXICILLIN-- HYDROCODONE BITARTRATE	22	136	1197	13	0.0101	0.0889	0.0010	0.0026	2956.28
21	ACETAMINOPHEN-- AZITHROMYCIN DIHYDRATE-- HYDROCODONE BITARTRATE	22	136	909	13	0.0101	0.0675	0.0010	0.0026	3892.92
22	ACETAMINOPHEN-- HYDROCODONE BITARTRATE--NAPROXEN	22	136	13	175	0.0101	0.0010	0.0130	0.0026	20220.93
23	BROMPHENIRAMINE MALEATE-- DEXTROMETHORPHAN HYDROBROMIDE-- PSEUDOEPHEDRINE HYDROCHLORIDE	22	-	2	0	-	0.0001	0.0000	0.0026	-
24	INSULIN GLARGINE-- IBUPROFEN--OMEPRazole	21	19	696	156	0.0014	0.0517	0.0116	0.0024	2894.88
25	ACETAMINOPHEN-- CEPHELEXIN-- HYDROCODONE BITARTRATE	18	136	202	13	0.0101	0.0150	0.0010	0.0021	14333.02
26	ACETAMINOPHEN-- CIPROFLOXACIN HYDROCHLORIDE-- OXYCODONE HYDROCHLORIDE	18	136	100	140	0.0101	0.0074	0.0104	0.0021	2688.46
27	ACETAMINOPHEN-- CYCLOBENZAPRINE HYDROCHLORIDE-- OXYCODONE HYDROCHLORIDE	18	136	125	140	0.0101	0.0093	0.0104	0.0021	2150.77
28	DIVALPROEX SODIUM-- LEVETIRACETAM-- OXCARBAZEPINE	18	34	71	17	0.0025	0.0053	0.0013	0.0021	124734.07
29	ACETAMINOPHEN-- AZITHROMYCIN DIHYDRATE--OXYCODONE HYDROCHLORIDE	16	136	909	140	0.0101	0.0675	0.0104	0.0019	262.90
30	ALBUTEROL SULFATE-- FLUTICASONE PROPIONATE-- MONTELUKAST SODIUM	16	556	86	95	0.0413	0.0064	0.0071	0.0019	1001.66

Figure 2: Relationship between active ingredient triples and occurrence and ER richness. Logarithms are in base 10.

Table 17: Top 30 TC1 drug class triples and their individual and co-occurrences probability, and occurrence richness ranked by ER total.

	TC1 drug class triples	Occ	part1-occ	part2-occ	part3-occ	p(three-occ)	p(part1-occ)	p(part2-occ)	p(part3-occ)	Occ-richness
1	Cardiovascular agents--Central nervous system agents-- Metabolic agents	1,376	10883	17160	5914	0.05	0.14	0.22	0.07	22.35
2	Central nervous system agents--Cardiovascular agents-- Metabolic agents	1,157	17160	10883	5914	0.04	0.22	0.14	0.07	18.79
3	Central nervous system agents--Cardiovascular agents-- Psychotherapeutic agents	648	17160	10883	3379	0.02	0.22	0.14	0.04	18.42
4	Anti-infectives--Central nervous system agents-- Psychotherapeutic agents	409	13495	17160	3379	0.01	0.17	0.22	0.04	9.37
5	Anti-infectives--Central nervous system agents-- Topical agents	489	13495	17160	6588	0.02	0.17	0.22	0.08	5.75
6	Anti-infectives--Central nervous system agents-- Respiratory agents	540	13495	17160	6407	0.02	0.17	0.22	0.08	6.53
7	Anti-infectives--Hormones/hormone modifiers--Respiratory agents	473	13495	8787	6407	0.02	0.17	0.11	0.08	11.17

8	Cardiovascular agents-- Gastrointestinal agents-- Metabolic agents	1,038	10883	2561	5914	0.04	0.14	0.03	0.07	112.95
9	Anti-infectives--Central nervous system agents-- Gastrointestinal agents	282	13495	17160	2561	0.01	0.17	0.22	0.03	8.53
10	Anti-infectives--Central nervous system agents-- Hormones/hormone modifiers	439	13495	17160	8787	0.02	0.17	0.22	0.11	3.87
11	Cardiovascular agents-- Coagulation modifiers-- Metabolic agents	525	10883	332	5914	0.02	0.14	0.00	0.07	440.66
12	Cardiovascular agents-- Hormones/hormone modifiers-- Metabolic agents	1,159	10883	8787	5914	0.04	0.14	0.11	0.07	36.76
13	Central nervous system agents--Gastrointestinal agents-- Psychotherapeutic agents	307	17160	2561	3379	0.01	0.22	0.03	0.04	37.08
14	Anti-infectives--Central nervous system agents-- Cardiovascular agents	283	13495	17160	10883	0.01	0.17	0.22	0.14	2.01
15	Central nervous system agents-- Hormones/hormone modifiers-- Psychotherapeutic agents	473	17160	8787	3379	0.02	0.22	0.11	0.04	16.65
16	Cardiovascular agents-- Central nervous system agents-- Psychotherapeutic agents	386	10883	17160	3379	0.01	0.14	0.22	0.04	10.97
17	Central nervous system agents-- Psychotherapeutic agents--Respiratory agents	271	17160	3379	6407	0.01	0.22	0.04	0.08	13.08
18	Coagulation modifiers-- Cardiovascular agents-- Metabolic agents	375	332	10883	5914	0.01	0.00	0.14	0.07	314.76
19	Cardiovascular agents-- Central nervous system agents--Gastrointestinal agents	228	10883	17160	2561	0.01	0.14	0.22	0.03	8.55
20	Anti-infectives-- Respiratory agents-- Topical agents	445	13495	6407	6588	0.02	0.17	0.08	0.08	14.01
21	Anti-infectives-- Cardiovascular agents-- Metabolic agents	490	13495	10883	5914	0.02	0.17	0.14	0.07	10.12
22	Central nervous system agents--Cardiovascular agents--Gastrointestinal agents	305	17160	10883	2561	0.01	0.22	0.14	0.03	11.44
23	Cardiovascular agents-- Metabolic agents -- Nutritional products	622	10883	5914	2258	0.02	0.14	0.07	0.03	76.76
24	Central nervous system agents-- Metabolic agents -- Psychotherapeutic agents	319	17160	5914	3379	0.01	0.22	0.07	0.04	16.68
25	Cardiovascular agents-- Metabolic agents -- Topical agents	652	10883	5914	6588	0.02	0.14	0.07	0.08	27.58

26	Cardiovascular agents-- Metabolic agents -- Psychotherapeutic agents	567	10883	5914	3379	0.02	0.14	0.07	0.04	46.76
27	Central nervous system agents--Respiratory agents--Topical agents	310	17160	6407	6588	0.01	0.22	0.08	0.08	7.68
28	Anti-infectives--Central nervous system agents-- Metabolic agents	208	13495	17160	5914	0.01	0.17	0.22	0.07	2.72
29	Central nervous system agents--Gastrointestinal agents-- Metabolic agents	204	17160	2561	5914	0.01	0.22	0.03	0.07	14.08
30	Anti-infectives-- Cardiovascular agents-- Central nervous system agents	158	13495	10883	17160	0.01	0.17	0.14	0.22	1.12

Table 18: Individual and joint probability of occurrence for the top 30 two-TC1 drug class polypharmacy (sorted by ER total) with richness of ER.

	TC1 drug class triples	ER	part1- EROcc	part2- EROcc	part3- EROcc	p(part1- ERocc)	p(part2- ERocc)	p(part 3- ERocc)	p(three- case-ER)	ER- richness
1	Cardiovascular agents--Central nervous system agents-- Metabolic agents	389	2245	6792	1049	0.104	0.315	0.049	0.039	24.55
2	Central nervous system agents-- Cardiovascular agents-- Metabolic agents	381	6792	2245	1049	0.315	0.104	0.049	0.038	24.05
3	Central nervous system agents-- Cardiovascular agents-- Psychotherapeutic agents	307	6792	2245	831	0.315	0.104	0.039	0.031	24.46
4	Anti-infectives-- Central nervous system agents-- Psychotherapeutic agents	297	4053	6792	831	0.188	0.315	0.039	0.030	13.11
5	Anti-infectives-- Central nervous system agents-- Topical agents	257	4053	6792	1492	0.188	0.315	0.069	0.026	6.32
6	Anti-infectives-- Central nervous system agents-- Respiratory agents	253	4053	6792	1647	0.188	0.315	0.076	0.025	5.63
7	Anti-infectives-- Hormones/hormone modifiers-- Respiratory agents	217	4053	1491	1647	0.188	0.069	0.076	0.022	22.01
8	Cardiovascular agents-- Gastrointestinal agents-- Metabolic agents	217	2245	714	1049	0.104	0.033	0.049	0.022	130.28

9	Anti-infectives-- Central nervous system agents-- Gastrointestinal agents	214	4053	6792	714	0.188	0.315	0.033	0.021	10.99
10	Anti-infectives-- Central nervous system agents-- Hormones/hormone modifiers	210	4053	6792	1491	0.188	0.315	0.069	0.021	5.16
11	Cardiovascular agents--Coagulation modifiers-- Metabolic agents	197	2245	119	1049	0.104	0.006	0.049	0.020	709.61
12	Cardiovascular agents-- Hormones/hormone modifiers-- Metabolic agents	194	2245	1491	1049	0.104	0.069	0.049	0.019	55.77
13	Central nervous system agents-- Gastrointestinal agents-- Psychotherapeutic agents	188	6792	714	831	0.315	0.033	0.039	0.019	47.09
14	Anti-infectives-- Central nervous system agents-- Cardiovascular agents	180	4053	6792	2245	0.188	0.315	0.104	0.018	2.94
15	Central nervous system agents-- Hormones/hormone modifiers-- Psychotherapeutic agents	166	6792	1491	831	0.315	0.069	0.039	0.017	19.91
16	Cardiovascular agents--Central nervous system agents-- Psychotherapeutic agents	148	2245	6792	831	0.104	0.315	0.039	0.015	11.79
17	Central nervous system agents-- Psychotherapeutic agents--Respiratory agents	147	6792	831	1647	0.315	0.039	0.076	0.015	15.96
18	Coagulation modifiers-- Cardiovascular agents-- Metabolic agents	143	119	2245	1049	0.006	0.104	0.049	0.014	515.10
19	Cardiovascular agents--Central nervous system agents-- Gastrointestinal agents	138	2245	6792	714	0.104	0.315	0.033	0.014	12.80
20	Anti-infectives-- Respiratory agents-- Topical agents	130	4053	1647	1492	0.188	0.076	0.069	0.013	13.18
21	Anti-infectives-- Cardiovascular agents-- Metabolic agents	128	4053	2245	1049	0.188	0.104	0.049	0.013	13.54

22	Central nervous system agents-- Cardiovascular agents-- Gastrointestinal agents	121	6792	2245	714	0.315	0.104	0.033	0.012	11.22
23	Cardiovascular agents-- Metabolic agents --Nutritional products	117	2245	1049	669	0.104	0.049	0.031	0.012	74.97
24	Central nervous system agents-- Metabolic agents -- Psychotherapeutic agents	115	6792	1049	831	0.315	0.049	0.039	0.012	19.61
25	Cardiovascular agents-- Metabolic agents --Topical agents	113	2245	1049	1492	0.104	0.049	0.069	0.011	32.46
26	Cardiovascular agents-- Metabolic agents -- Psychotherapeutic agents	103	2245	1049	831	0.104	0.049	0.039	0.010	53.13
27	Central nervous system agents-- Respiratory agents-- Topical agents	103	6792	1647	1492	0.315	0.076	0.069	0.010	6.23
28	Anti-infectives-- Central nervous system agents-- Metabolic agents	91	4053	6792	1049	0.188	0.315	0.049	0.009	3.18
29	Central nervous system agents-- Gastrointestinal agents-- Metabolic agents	90	6792	714	1049	0.315	0.033	0.049	0.009	17.86
30	Anti-infectives-- Cardiovascular agents--Central nervous system agents	85	4053	2245	6792	0.188	0.104	0.315	0.009	1.39

Figure 3: Relationship between TC1 drug class triples and occurrence and ER richness. Logarithms are in base 10.

Table 19: Top 30 TC1S1 drug class triples and their individual and co-occurrences probability, and occurrence richness ranked by ER total.

	TC1S1 drug class triples	Occ	part1-occ	part2-occ	part3-occ	p(part1-occ)	p(part2-occ)	p(part3-occ)	p(three-occ)	Occ-richness
1	ADRENAL_CORTICAL_STEROIDS--BRONCHODILATORS--MACROLIDE_DERIVATIVES	77	781	2683	3357	0.01	0.04	0.05	0.003	154.58
2	ANALGESICS--ANTICONVULSANTS--MUSCLE_RELAXANTS	66	8519	1280	441	0.12	0.02	0.01	0.003	193.82
3	ANALGESICS--ANTIDEPRESSANTS--ANXIOLYTICSEDATIVESAND_HYPNOTICS	23	8519	2798	637	0.12	0.04	0.01	0.001	21.39
4	ADRENAL_CORTICAL_STEROIDS--BRONCHODILATORS--PENICILLINS	56	781	2683	5593	0.01	0.04	0.08	0.002	67.48
5	ANALGESICS--PENICILLINS--UPPER_RESPIRATORY_COMBINATIONS	66	8519	5593	822	0.12	0.08	0.01	0.003	23.80
6	ANTIDIABETIC_AGENTS--ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS--ANTIHYPERTENSIVE_AGENTS	185	2079	2005	2931	0.03	0.03	0.04	0.007	213.83
7	ANALGESICS--ANTICONVULSANTS--ANTIDEPRESSANTS	33	8519	1280	2798	0.12	0.02	0.04	0.001	15.27

8	ANTIDIABETIC_AGENTS-- ANGIOTENSIN_CONVERTING_ ENZYME_INHIBITORS-- BETA_ADRENERGIC_BLOCKING_ AGENTS	43	2079	2005	1103	0.03	0.03	0.02	0.002	132.07
9	BRONCHODILATORS-- LEUKOTRIENE_MODIFIERS-- RESPIRATORY_INHALANT_PRODUCTS	62	2683	457	200	0.04	0.01	0.00	0.002	3570.34
10	ANALGESICS--IRON_PRODUCTS-- LAXATIVES	31	8519	1013	268	0.12	0.01	0.00	0.001	189.28
11	ANALGESICS--ANTIDEPRESSANTS-- MUSCLE_RELAXANTS	46	8519	2798	441	0.12	0.04	0.01	0.002	61.80
12	BETA_ADRENERGIC_BLOCKING_ AGENTS--DIURETICS-- MUSCLE_RELAXANTS	2	1103	716	441	0.02	0.01	0.01	0.000	81.09
13	ANALGESICS-- ANTIEMETIC/ANTIVERTIGO_AGENTS- -MUSCLE_RELAXANTS	15	8519	724	441	0.12	0.01	0.01	0.001	77.88
14	ANALGESICS-- MACROLIDE_DERIVATIVES-- PENICILLINS	30	8519	3357	5593	0.12	0.05	0.08	0.001	2.65
15	ANALGESICS--MUSCLE_RELAXANTS-- PROTON_PUMP_INHIBITORS	41	8519	441	1429	0.12	0.01	0.02	0.002	107.85
16	ANGIOTENSIN_CONVERTING_ ENZYME_INHIBITORS-- BETA_ADRENERGIC_BLOCKING_ AGENTS--DIURETICS	86	2005	1103	716	0.03	0.02	0.01	0.003	766.97
17	ANALGESICS--ANTIDEPRESSANTS-- ANTICONVULSANTS	39	8519	2798	1280	0.12	0.04	0.02	0.001	18.05
18	ANALGESICS--MUSCLE_RELAXANTS-- PENICILLINS	21	8519	441	5593	0.12	0.01	0.08	0.001	14.11
19	ANTIDIABETIC_AGENTS-- ANALGESICS-- PROTON_PUMP_INHIBITORS	9	2079	8519	1429	0.03	0.12	0.02	0.000	5.02
20	ANTIHYPERTENSIVE_COMBINATIONS --BETA_ADRENERGIC_BLOCKING_ AGENTS-- CALCIUM_CHANNEL_BLOCKING_ AGENTS	44	1925	1103	804	0.03	0.02	0.01	0.002	363.98
21	BETA_ADRENERGIC_BLOCKING_ AGENTS-- CALCIUM_CHANNEL_BLOCKING_ AGENTS--DIURETICS	40	1103	804	716	0.02	0.01	0.01	0.002	889.61
22	ADRENAL_CORTICAL_STEROIDS-- BRONCHODILATORS-- RESPIRATORY_INHALANT_PRODUCTS	29	781	2683	200	0.01	0.04	0.00	0.001	977.20
23	ANALGESICS-- ANTIEMETIC/ANTIVERTIGO_AGENTS- -PENICILLINS	24	8519	724	5593	0.12	0.01	0.08	0.001	9.82
24	ANALGESICS--OTIC_PREPARATIONS-- PENICILLINS	21	8519	350	5593	0.12	0.00	0.08	0.001	17.78
25	ANALGESICS-- ANTIEMETIC/ANTIVERTIGO_AGENTS- -MACROLIDE_DERIVATIVES	17	8519	724	3357	0.12	0.01	0.05	0.001	11.59
26	ANALGESICS--BRONCHODILATORS-- RESPIRATORY_INHALANT_PRODUCTS	22	8519	2683	200	0.12	0.04	0.00	0.001	67.96
27	ANALGESICS--CEPHALOSPORINS-- MISCELLANEOUS_ANTIBIOTICS	16	8519	871	544	0.12	0.01	0.01	0.001	55.98
28	ANTICOAGULANTS-- ANTIARRHYTHMIC_AGENTS-- BETA_ADRENERGIC_BLOCKING_ AGENTS	15	256	398	1103	0.00	0.01	0.02	0.001	1884.85

29	ADRENAL_CORTICAL_STEROIDS-- BRONCHODILATORS--QUINOLONES	15	781	2683	393	0.01	0.04	0.01	0.001	257.22
30	ANALGESICS--IRON_PRODUCTS-- VITAMINS	16	8519	1013	483	0.12	0.01	0.01	0.001	54.21

Table 20: Individual and joint probability of occurrence for the top 30 two-TC1S1 drug class polypharmacy (sorted by ER total) with richness of and ER.

	TC1S1 drug class triples	ER	part1-EROcc	part2-EROcc	part3-EROcc	p(part1-ERocc)	p(part2-ERocc)	p(part3-ERocc)	p(three-case-ER)	ER-richness
1	ADRENAL_CORTICAL_STEROIDS-- BRONCHODILATORS-- MACROLIDE_DERIVATIVES	52	302	723	932	0.02	0.04	0.05	0.01	160.16
2	ANALGESICS-- ANTICONSULSANTS-- MUSCLE_RELAXANTS	45	3973	505	166	0.23	0.03	0.01	0.01	84.69
3	ANALGESICS-- ANTIDEPRESSANTS-- ANXIOLYTICSSEDATIVES AND_HYPNOTICS	43	3973	575	160	0.23	0.03	0.01	0.01	73.74
4	ADRENAL_CORTICAL_STEROIDS-- BRONCHODILATORS-- PENICILLINS	37	302	723	1591	0.02	0.04	0.09	0.00	66.76
5	ANALGESICS-- PENICILLINS-- UPPER_RESPIRATORY_COMBINATIONS	30	3973	1591	150	0.23	0.09	0.01	0.00	19.83
6	ANTIDIABETIC_AGENTS -- ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- ANTIHYPERLIPIDEMIC_AGENTS	29	406	329	282	0.02	0.02	0.02	0.00	482.55
7	ANALGESICS-- ANTICONSULSANTS-- ANTIDEPRESSANTS	28	3973	505	575	0.23	0.03	0.03	0.00	15.21
8	ANTIDIABETIC_AGENTS -- ANGIOTENSIN_CONVERTING_ENZYME_INHIBITORS-- BETA_ADRENERGIC_BLOCKING_AGENTS	26	406	329	196	0.02	0.02	0.01	0.00	622.46
9	BRONCHODILATORS-- LEUKOTRIENE_MODIFIERS-- RESPIRATORY_INHALANT_PRODUCTS	26	723	97	63	0.04	0.01	0.00	0.00	3688.42
10	ANALGESICS-- IRON_PRODUCTS-- LAXATIVES	25	3973	394	91	0.23	0.02	0.01	0.00	110.00
11	ANALGESICS-- ANTIDEPRESSANTS-- MUSCLE_RELAXANTS	24	3973	575	166	0.23	0.03	0.01	0.00	39.67
12	BETA_ADRENERGIC_BLOCKING_AGENTS-- DIURETICS-- MUSCLE_RELAXANTS	24	196	164	166	0.01	0.01	0.01	0.00	2819.17
13	ANALGESICS-- ANTIEMETIC/ANTIVERTIGO_AGENTS-- MUSCLE_RELAXANTS	23	3973	420	166	0.23	0.02	0.01	0.00	52.04

14	ANALGESICS-- MACROLIDE_ DERIVATIVES-- PENICILLINS	23	3973	932	1591	0.23	0.05	0.09	0.00	2.45
15	ANALGESICS-- MUSCLE_RELAXANTS-- PROTON_PUMP_ INHIBITORS	23	3973	166	315	0.23	0.01	0.02	0.00	69.39
16	ANGIOTENSIN_CONVERTING_ENZYME_ INHIBITORS-- BETA_ADRENERGIC_BLOCKING_AGENTS-- DIURETICS	23	329	196	164	0.02	0.01	0.01	0.00	1363.17
17	ANALGESICS-- ANTIDEPRESSANTS-- ANTICONVULSANTS	22	3973	575	505	0.23	0.03	0.03	0.00	11.95
18	ANALGESICS-- MUSCLE_RELAXANTS-- PENICILLINS	22	3973	166	1591	0.23	0.01	0.09	0.00	13.14
19	ANTIDIABETIC_AGENTS-- ANALGESICS-- PROTON_PUMP_ INHIBITORS	21	406	3973	315	0.02	0.23	0.02	0.00	25.90
20	ANTIHYPERTENSIVE_COMBINATIONS-- BETA_ADRENERGIC_BLOCKING_AGENTS-- CALCIUM_CHANNEL_BLOCKING_AGENTS	21	242	196	114	0.01	0.01	0.01	0.00	2434.22
21	BETA_ADRENERGIC_BLOCKING_AGENTS-- CALCIUM_CHANNEL_BLOCKING_AGENTS-- DIURETICS	21	196	114	164	0.01	0.01	0.01	0.00	3591.96
22	ADRENAL_CORTICAL_STEROIDS-- BRONCHODILATORS-- RESPIRATORY_INHALANT_PRODUCTS	20	302	723	63	0.02	0.04	0.00	0.00	911.30
23	ANALGESICS-- ANTIEMETIC/ANTIVERTIGO_AGENTS-- PENICILLINS	20	3973	420	1591	0.23	0.02	0.09	0.00	4.72
24	ANALGESICS-- OTIC_PREPARATIONS-- PENICILLINS	20	3973	86	1591	0.23	0.00	0.09	0.00	23.06
25	ANALGESICS-- ANTIEMETIC/ANTIVERTIGO_AGENTS-- MACROLIDE_DERIVATIVES	19	3973	420	932	0.23	0.02	0.05	0.00	7.66
26	ANALGESICS-- BRONCHODILATORS-- RESPIRATORY_INHALANT_PRODUCTS	19	3973	723	63	0.23	0.04	0.00	0.00	65.81
27	ANALGESICS-- CEPHALOSPORINS-- MISCELLANEOUS_ANTIBIOTICS	19	3973	290	203	0.23	0.02	0.01	0.00	50.92
28	ANTICOAGULANTS-- ANTIARRHYTHMIC_AGENTS-- BETA_ADRENERGIC_BLOCKING_AGENTS	19	102	77	196	0.01	0.00	0.01	0.00	7736.14
29	ADRENAL_CORTICAL_STEROIDS-- BRONCHODILATORS-- QUINOLONES	17	302	723	141	0.02	0.04	0.01	0.00	346.10
30	ANALGESICS-- IRON_PRODUCTS-- VITAMINS	17	3973	394	89	0.23	0.02	0.01	0.00	76.48

Figure 4: Relationship between TC1S1 drug class triples and occurrence and ER richness. Logarithms are in base 10.