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Association Rule Mining of Polypharmacy Drug Utilization Patterns in Health Care Administrative Data Using SAS[®] Enterprise Miner™

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ABSTRACT

Pediatric polypharmacy is prevalent in the both outpatient and inpatient setting, and is associated with increased exposure to adverse drug events (ADEs). The current definition of polypharmacy is simply a count of concurrent medication exposures for a given patient being equally to or greater than five, but this patient-level approach does not offer insights regarding the reasons why polypharmacy occurs that could be gained by a complementary drug-level approach, examining polypharmacy patterns not only across patients but also across medications. Health care administrative databases offer opportunities to examine drug-level relationships and patterns. Association rule mining (ARM) is a well-established data mining technique that has been commonly used for mining commercial transactional databases. Link Analysis (LA) is a popular social network analysis technique that is used to discover and visualize associations between different items. We transformed administrative data to a transaction data format suitable for mining rules and applied ARM and LA to analyze drug utilization and polypharmacy patterns in health care administrative database using SAS® Enterprise Miner[™]. Our results demonstrate how ARM can find co-utilization associations among drugs, thereby enabling the description of various polypharmacy patterns, and the subsequent detection of patient characteristics associated with these patterns. We believe that ARM and LA, along with their visualization graphics, provide valuable methods to analyze drug utilization and polypharmacy, and that this approach could be used in mining other databases such as administrative claims data and electronic medical records.

Key Words: polypharmacy; adverse drug events; health care administrative databases; association rule mining; link analysis; data visualization; Pharmacoepidemiology

INTRODUCTION

Polypharmacy, typically defined as exposure of a patient to 5 or more medications concurrently, is known to pose an increased hazard to patients of experiencing an adverse drug event (ADE) [1]. ADEs are major cause of increased morbidity, mortality, and health care costs: ADEs are ranked as the 4th-to-6th leading causes of death in inpatients [1,2], and in the United States, for every dollar spent on medication in 2000, more than a dollar was estimated to have been spent on direct medical costs related to drug misadventures [3]. Although often considered to be of most concern for the elderly, polypharmacy is common among pediatric patients in the United States [4-6], resulting in many patients who are treated with polypharmacy regimens, especially for children with complex chronic conditions, being exposed to multiple potential drug-drug interactions [5].

Currently the prevailing method of assessing polypharmacy is simply a count the number of generic drug concurrently used by patients [4-6]. This patient-level approach offers a limited range of insight regarding why polypharmacy occurs, since the combinations of particular drugs is lost by the simplicity of a single number for each patient. We therefore sought to examine polypharmacy from a drug-level analytic approach. Specifically, we considered how data mining could be applied, as this methodology offers great potential for drug safety analytics [7,9]. For example, Chen et al. applied association rule mining (ARM) to a linked dataset comprised of a pharmaceutical prescribing dataset and a hospital admissions dataset in order to identify groups of patients who are more likely to have an ADE to ACE inhibitors [8]. Zhu et al performed clinical trial safety data analytics using ARM [9]. Harpaz et al. mined muti-item drug ADEs associations in spontaneous reporting systems [10]. To date, data mining approaches have mostly focused on identifying associations between specific drugs and either specific ADE or specific clusters ADEs.

In this paper we describe our application of ARM and LA in health care administrative databases to analyze and visualize polypharmacy drug utilization patterns at the drug-level en mass, and then to

examine the association of different polypharmacy patterns with patient demographic and clinical characteristics.

ASSOCIATION RULES AND DRUG UTILIZATION

ARM finds interesting association or correlation relationships among a large set of data items. With massive amounts of data continuously be stored in databases and available, many industries are becoming interested in mining association rules from their databases. ARM was initially used for market basket analysis, where interested lies in finding associations between the different items that customers place in their "shopping baskets" as recorded in commercial transaction databases. The discovery of such associations can help retailers develop marketing strategies by gaining insight into which items are frequently purchased together by customers. We applied ARM in clinical administrative databases to analyze drug utilization patterns and polypharmacy, polypharmacy associated certain medical conditions, or certain patient subpopulations.

The basic concepts of AMR were established originally on transaction data. Initially AMR was implemented by Agarwal et al [11,12]. ARM has been divided into two phases of process as follows: Phase 1: Identify the sets of frequent items or itemsets or pattern within the set of transaction using user-specified support threshold. Phase 2: Generate inferences or rules from these above patterns using user-specified confidence threshold. The above two phases are generated strong association rules from dataset. The first phase is called frequent itemset construction or mining. That is extremely computational expensive than phase 2. The second phase is called association rule generation. That is, straight forward process. In a given database, denote $I = \{i1, i2, ..., ik\}$ as a set of k distinct items. A set of items is also called as an itemset. An association rule (AR) is a pair (A, B) of sets of items, denoted by $A \rightarrow B$. A is the antecedent and B is the consequent of the rule $A \rightarrow B$. The essential parameters associated to an AR are its support and confidence. The support measures the "prevalence" of A U B. It is defined as the fraction of transactions in the database which contain all items in a specific rule. This can be written as:

Support (A
$$\rightarrow$$
 B) = $\frac{\#\{A \cup B\}}{N}$

Where #{A U B} is the number transactions (itemset) which contain both A and B and N represents the total number of transactions (itemset) in the database. The confidence measures the "predictability" of the rule:

Confidence
$$(A \longrightarrow B) = \frac{\text{Support } (A \longrightarrow B)}{\text{Support } (A)} = \frac{\#\{A \cup B\}}{\#\{A\}}$$

Clearly, the confidence of $A \rightarrow B$ is an estimation of probability that a record that contains the items A, chosen at random, will contain the items B. Where $\#\{A\}$ is the number transactions (itemset) which contain A. Another measure of the rule is lift.

Lift
$$(A \rightarrow B) = \frac{\text{Confidence } (A \rightarrow B)}{\text{Expected Confidence } (A \rightarrow B)} = \frac{\#\{A \cup B\} \times N}{\#\{A\} \times \#\{B\}}$$

Lift is the ratio of the confidence of a rule to the expected confidence of the rule. The expected confidence is calculated under the assumption that the left hand side of a rule is independent from the right hand side of the rule. Consequently, lift is a measure of association between left hand side and right hand side of the rule. Values that are greater than one represents positive association between A and B. Values that are equal to one represent A and B are independent. Values that are less than one represents negative association between A and B. The lift serves as a reference to interpret the importance of the AR.

In the transaction data, for the rule A \rightarrow B, the itemsets A and B can be both regarded as certain events, and the rule describes how the event B is associated with the event A, i.e., how the occurrence of event A could imply the occurrence of event B. In the setting of clinical administrative data, the rule A \rightarrow B can be mined using different aspect of the databases to answer many important pharmacoepidemiology questions, such as all specific drug use in specific population, specific drug polypharmacy,

polypharamacy associated medical conditions, procedures and ADEs. The rules should not be interpreted as a direct causation, but as an association between two or more drugs. AR does not create rules about repeating items, such as "if item A is part of an event, then another item A is also part of the event X% of the time." In association analysis, it does not matter whether an individual patient takes one or multiple pills of drug A in the day; only the administration of drug A in the prescription is relevant. However, identifying creditable associations between two or more specific drugs (drug-drug combination or polypharmacy) can help clinicians make decisions such as when to choose which medications to adjust, when they intend to escalate or de-escalate medications as a patient's condition or stage changes.

LINK ANALYSIS

LA, also known as Social Network Analysis, is a mathematical and graphical analysis highlighting the linkage between items (objects), including drugs, medical conditions, organizations, people and transactions. LA is used to identify and visualize the associations (links) between different items and discover item clusters and has been used for investigation of criminal activity (fraud detection, counterterrorism, and intelligence), computer security analysis, search engine optimization, market research, medical research, and art [13]. The Link Analysis node in SAS Enterprise Miner provides a very powerful but easy to use platform for performing LA and visualize the results in a succinct manner. The Link Analysis node processes transactional data in the following steps [14,15]:

- 1. The node first discovers association or sequence rules computing confidence, support, expected confidence and lift using equations stated above.
- 2. The link analysis node then transforms the rules data into a network graph data in the form of nodes and links where the support of each item becomes the node weight and the strength of the association (confidence of the rule) becomes the link weight. The two-item sequence rules are transformed into a directed graph data and the association rules into an undirected graph data.
- 3. The node calculates several centrality measures and detects item clusters from the link graph.
- 4. Finally, it scores the transactional data. There are two score properties under the link analysis node. The node can either produce a next-best-offer list using the association /sequence rules or produce customer segmentation information for scoring using the item clusters.

There are some overlaps on association or sequence rules discovery between AR and LA. For more information, see the SAS Enterprise Miner: References Help. In this paper, we applied ARM to analyze drug utilization and polypharmacy and used LA to visualize the drug-drug combination patterns.

METHODS

DATA SOURCES

This study used the Pediatric Health Information System (PHIS) database, a national health care administrative database containing resource utilization data for pediatric inpatient, emergency department, ambulatory surgery, and observation unit patient encounters from 49 not-for-profit, tertiary care pediatric hospitals in the US, representing most major U.S. metropolitan areas and approximately 85% of freestanding pediatric acute care hospital admissions in the United States [16]. These participating hospitals are located in 32 US states and the District of Columbia. All these hospitals are affiliated with the Children's Hospital Association (CHA, Kansas City, KS), a national business alliance of children's hospitals. The PHIS database includes patient demographics, diagnosis, and procedures as well as detailed pharmacy information, including ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes, CPT (Current Procedural Terminology) codes, and CTC (Clinical Transaction Classification) codes for each diagnosis, procedure, generic drug entity dispensed, and clinical services for each day of hospital stay of each patient (Figure 1). Each patient in PHIS is assigned a unique identifier allowing records to be linked among different datasets and longitudinally linked. Details about the PHIS database have been reported previously [4,5]. A joint effort between participating hospitals, a data manager (Truven Health Care Analytics, IBM), and the CHA ensures maintenance of data quality and reliability. PHIS is a relational database and all data in PHIS are deidentified. Our study included all children <18 years of age, who admitted to ED, and were discharged from participating hospitals between 1 January 2014, and 31 December 2014.

Patient Abstract and Medical Coding

Health Care Resource Utilization Data

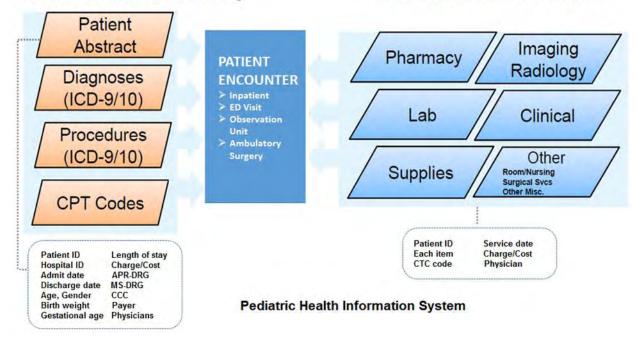


Figure 1. PHIS Databases

DATA PREPARATION

In this project, we used only two datasets in the databases. One is Patient Abstract, which contains demographic characteristics, up to 41 diagnosis codes, and up to 25 procedure codes; the other one is Pharmacy which contains detail daily drug use including service date, drug name, dose, route of administration, and charges. We first cleaned the data, corrected data errors, removed some duplicates, and made service day variable consistent cross all hospitals. For these two data, we selected only variables we needed. Then we mapped the administrative datasets to transactional data formats. The process consisted of three steps. (1). drug names were mapped to their corresponding generic names to reduce drug naming redundancy and reduce computing time. We implemented this by using previously developed PHIS drug dictionary [4]. There are 28 variables in the pharmacy data, we kept only Patient_ID, Service_Day, Generic_Name (Table 1). The variable Service_Day identifies the sequence in which the drugs were used. In this example, all the drugs were used at the same day. We do not know the order in which the drugs were administered by nurses. When the sequence is taken into account, association analysis is known as sequence analysis. Sequence analysis is not demonstrated in this paper. (2). For the purpose of this study, we selected only Patient ID, age, and up to 41 diagnoses from the Patient Abstract data (Table 2). Patient records data were then transformed into transactional format (Table 3). (3). Create the work dataset by combining all generated data (Table 1 and Table 3). All data management were conducted by using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Table 1: Pharmacy Data

Patient ID	Service Day	Generic Name
P0000001	1	Acetaminophen
P0000001	1	Albuterol sulfate
P0000001	1	Amoxicillin trihydrate

P00000001	1	Ceftriaxone sodium
P00000001	1	Dexamethasone
P00000001	1	Prednisolone
P0000002	1	Acetaminophen
P0000002	1	Heparin sodium
P0000002	1	Lidocaine HCI
P0000002	1	Morphine sulfate
P0000003	1	Albuterol sulfate
P0000003	1	Ibuprofen
P00010000	1	Ibuprofen

Table 2: Patient Diagnosis (Administrative data format)

Patient ID	Count_DX	DX1	DX2	DX3	 DX41
P00000001	3	Asthma	Otitis Media	Vomiting	
P00000002	3	Headache	Abdominal pain	Acute lymphoid leukemia	
P00000003	2	Acute bronchitis	Unspecified viral infection		
P00010000	1	Pharyngitis			

Table 3: Patient Diagnosis (Transactional data format)

Patient ID	DX
P00000001	Asthma
P00000001	Otitis Media
P00000001	Vomiting
P00000002	Headache
P00000002	Abdominal pain
P00000002	Acute lymphoid leukemia
P0000003	Acute bronchitis
P0000003	Unspecified viral infection
P00010000	Pharyngitis

Patient ID	Rx DX
P00000001	Acetaminophen
P00000001	Albuterol sulfate
P00000001	Amoxicillin trihydrate
P00000001	Ceftriaxone sodium
P00000001	Dexamethasone
P00000001	Prednisolone
P00000001	Acetaminophen
P00000001	Asthma
P00000001	Otitis Media
P00000001	Vomiting
P0000002	Acetaminophen
P0000002	Heparin sodium
P0000002	Lidocaine HCI
P0000002	Morphine sulfate
P00000002	Acetaminophen
P0000002	Abdominal pain
P0000002	Acute lymphoid leukemia
P0000003	Albuterol sulfate
P0000003	Ibuprofen
P0000003	Acute bronchitis
P0000003	Unspecified viral infection
P00010000	Ibuprofen
P00010000	Pharyngitis

Table 4: Patient Diagnosis and Drug Use (work data)

RUN THE ASSOCIATION NODE AND THE LINK ANALYSIS NODE

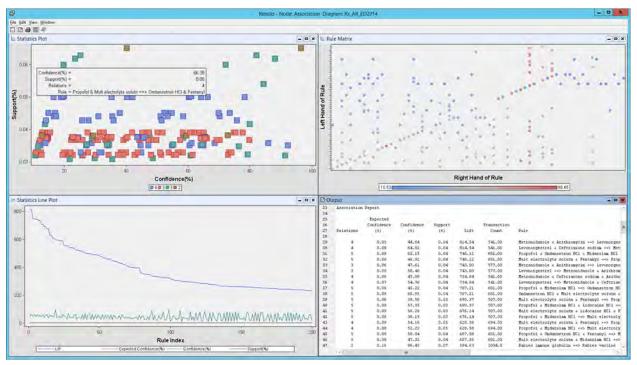
Observe the Association properties subgroup of the Association node (SAS[®] Enterprise Miner[™]14.2, SAS Institute Inc., Cary, NC). These properties determine how large each association can be and how association rules are formed. Set the value of the Maximum Items property to 5. This indicates that only associations among up to five drugs are generated. In many drug safety reports, some specific drug led to clinical side effects or one or more ADEs. ADEs can involve single or multiple drugs and describe single or multiple adverse drug interactions. Our previous studies that ≥3 drug combinations are very common [4,5]. A greater number of drugs used concurrently may have a potentially multiplicative increase in the number of ADEs, especially for specific drug classes such as sedation [17] or QT-prolonging medications [18].In the absence of a gold standard (the set of all true multi-drug combinations and the frequency of the combinations are unknown) which would have enabled us to calibrate or determine the

most appropriate thresholds in a quantitative manner, we resorted to a data driven and heuristic approach guided by clinical expert knowledge. The support threshold was set high enough value to highlight the more frequent drug-drug combination patterns. Setting the threshold to a lower value resulted in a much larger set of associations. We set the threshold as support $\geq 0.01\%$ in this example. As we discussed in previous section, The Confidence for the rule is the conditional probability that drug B is in the prescription given that drug A is present. Rules with highest confidence and support percentages are recommended to discover high correlation items. Our objective is to find more specific drug-drug combinations which may pose a risk for ADEs, so we set Confidence threshold as 1% in this example.

We set the thresholds for both support and confidence same as running the Association Node. The remaining properties are set to the default. Once the settings are completed, connect the input data node with the Association node and the Link Analysis node respectively and run the project.

RESULTS

The Results window of the Association node shows the association statistics (Display 1). When one click any square (color coded based on the number of drug-drug combination, brown means 2 drugs combination, green 3, blue 4, red 5), the window displays the rule and the two association parameters: support and confidence.



Display 1. The Association Statistics

In the Results window of the Association node, select View \Rightarrow Rules \Rightarrow Rule Table from the main menu, it will display the Rules Table (Display 2). The Rules Table displays information about each rule that was created. This includes the rule, support, confidence, expected confidence, lift, number of occurrence, and the items in the rule. For this project, the rule is the drug-drug combination (polypharmacy). The number of occurrence is the number of patients, who were exposed to the drug-drug combination. The support can be used as proportion or prevalence of the drug combination exposed in the population. The Rule Table can be used to screen the drug-drug combinations which have a risk for drug-drug interactions and lead to ADEs. We listed top 5 most common two to five drugs combination exposed among pediatric patients in ED visits in the U.S.A. 2014 (Table 5).

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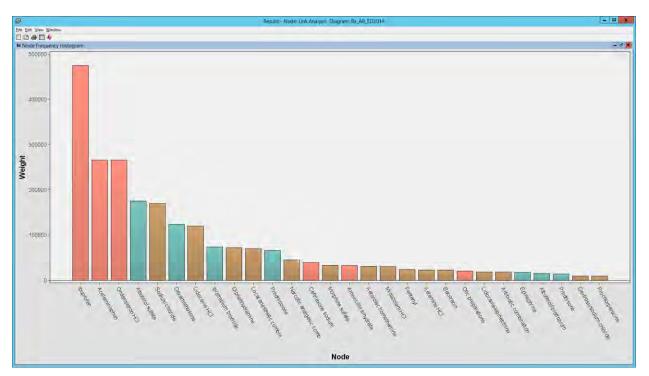
Display 2. Table of association rules from ARM

Table 5. Top 5 most common two to five drug-drug combinations exposed among Sick Children in
ED Visits in the US Children's Hospitals, 2014

Drug-drug Combinations	Number of Patients Exposed	%, Exposed
Two drug combinations (D2)		
Albuterol sulfate & Ipratropium bromide	72,956	2.37
Albuterol sulfate & Prednisolone	43,769	1.42
Albuterol sulfate & Dexamethasone	42,171	1.37
Ibuprofen + Ondansetron HCI	40,070	1.30
Acetaminophen + Ibuprofen	39,488	1.28
Three drug combinations (D3)		
Albuterol sulfate & Ipratropium bromide & Prednisolone	26,805	0.87
Albuterol sulfate & Dexamethasone & Ipratropium bromide	26,175	0.85
Lidocaine HCI & Ondansetron HCI & Sodium chloride	11,376	0.37
Albuterol sulfate & Ibuprofen & Ipratropium bromide	9,292	0.27
Acetaminophen & Ibuprofen & Ondansetron HCI	6,959	0.23
Four drug combinations (D4)		
Diphenhydramine & Ketorolac tromethamine & Prochlorperazine & Sodium chloride	3,326	0.11
Albuterol sulfate & Ipratropium bromide & Prednisolone &	3,017	0.10

Sodium chloride		
Albuterol sulfate & Ibuprofen & Ipratropium bromide & Prednisolone	2,901	0.10
Albuterol sulfate & Ipratropium bromide & Ibuprofen & Dexamethasone	2,587	0.09
Albuterol sulfate & Acetaminophen & Dexamethasone & Ipratropium bromide	2,341	0.08
Five drug combinations (D5)		
Diphenhydramine & Ketorolac tromethamine & Lidocaine HCI & Prochlorperazine & Sodium chloride	1,433	0.05
Fentanyl & Midazolam HCl & Mult electrolyte solutn & Ondansetron HCl & Propofol	601	0.03
Fentanyl & Lidocaine HCl & Midazolam HCl & Ondansetron HCl & Propofol	580	0.02
Fentanyl & Lidocaine HCI & Midazolam HCI & Mult electrolyte solutn & Ondansetron HCI	574	0.02
Fentanyl & Lidocaine HCI & Mult electrolyte solutn & Ondansetron HCI & Propofol	566	0.02

In the Results window the Link Analysis node, select View \Rightarrow Plots \Rightarrow Node Frequency Histogram (by item cluster) from the main menu, it will display the Node Frequency Histogram (Display 3), which shows frequency of specific drug utilization. The weight represents number of patients who took the particular drug. One can see that ibuprofen is the most common drug used among pediatric patients in ED visits.



Display 3: Node Frequency Histogram

The prevalence of drug use can be calculated by dividing the number of patients who had used the certain drug by total number of patients in the cohort. The top 12 most commonly used drugs listed in Table 6.

Generic Drug Name	Number of Patients Exposed	%, Exposed
Ibuprofen	474,589	15.43
Acetaminophen	265,448	8.63
Ondansetron HCI	265,355	8.62
Albuterol sulfate	174,998	5.69
Sodium chloride	169,930	5.52
Dexamethasone	123,520	4.02
Lidocaine HCI	120,244	3.91
Ipratropium bromide	73,605	2.39
Diphenhydramine	72,182	2.34
Prednisolone	66,408	2.16
Ceftriaxone sodium	39330	1.28
Morphine sulfate	33429	1.09

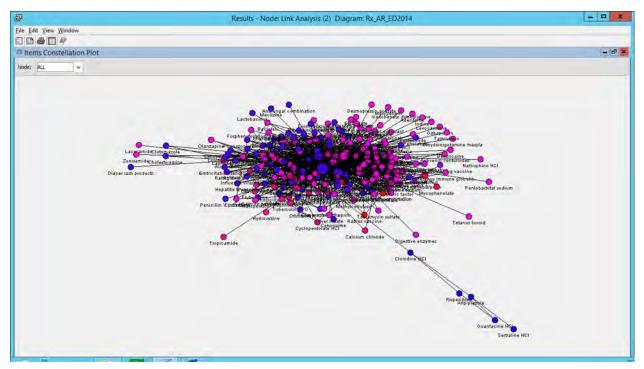
Table 5. Top dozen most common drug used among Sick Children in ED Visits in the US
Children's Hospitals, 2014

In the results window of the Link Analysis node, users can find view a table of association rules. Below is a screenshot of part of the rule table (Display 4). We will take rule 6 as example to illustrate how to read this table. The expected confidence of rule 6 is 8.01%, indicating that epinephrine will be exposed to 8.01% of the patients who have ED visits and a support of 0.72% indicates that epinephrine and dexamethasone are used together by 0.72% of patients during the ED visit. When a patient already took epinephrine, he/she has a 63.76% of chance to also take dexamethasone as shown by the confidence, which is 7.69 times the chance of taking dexamethasone within the population, shown by the lift value of 7.69. This information can be useful to understanding drug utilization patterns. LA can generate only two item (drug) association rules. This table is similar to the Rules Table (Relations = 2) in the results window of the Association Node (Display 2), which can generate two or more item association rules.

2					Result	- Node: Link Analysis Diagram: Rx_AR_ED2014		- 0
ie Edit Yiew Wins	dow							
Dest								
the state of the s	atistics by Rule ID							
	1	(annual second	12/2/10/20	-	122	6	Ibaconar	100000
ule ID	Relations	Expected Confidence(%)	Confidence(%)	Support(%)	Ut	Transaction Count Rule	Let Hard of Rule	Recommended terms
	1	2 113			73 8.73		Ipratropium bromide	Albuterol sulfate
		2 11.0			42 6.38		Prochlorperazine	Sodium chloride
	1	2 113			42 04.04 84 5.81		Prochlorperadine Prednisolone	Ketorolac tromethamine Albuterol suitate
	1	2 45			40 14.00		Prochlorperazine	Diphenhydramine
	1	2 80			72 7.90		Epinephrine	Dexamethasone
	1	2 11.3			53 5.25		Prednisone	Albuferol sulfate
	1	2 1100			12 5.07		Ketorolac tromethamine	Sodium chloride
	9	2 11.02			33 496		Dextrose/sodium chloride	Sodium chloride
	10	2 43			52 12.10		Albuteroliforatropium	Prednisolone
	11	2 17.2			63 2.48		Ketamine HCI	Ondansetron HCI
	12	2 47			73 8.73		Albuterol sulfate	Ipratropium bromide
	13	2 47	1 4	1.60 1	75 8.51		Prednisolone	Ipratropium bromide
	14	2 45			46 8.76		Lidocaine/epinephrine	Local anesthetic combin
	15	2 110			83 3.49		Morphine sulfate	Sodium chloride
	16	2 45			55 8.37		Baotracin	Local anesthetic combin
	17	2 47			34 7.88		Prednisone	Ipratropium bromide
	11	2 43			75 0.51		Ipratropium bromide	Prednisolone
	19	2 17.2			79 2.12		Morphine sulfate	Ondansetron HCI
	20	2 11.3		.34 0.			Albuterolifpratropium	Albuterol sulfate
	21	2 80			71 4.47		Ipratropium bromide	Dexamethasone
	22	2 7.8			53 4.95		Ketamine HCI	Lidocaine HCI
	23	2 45			41 7.75		Antibiotic combination	Local anesthetic combin
	24	2 11.3			73 3.01		Dexamethasone	Albuferol sulfate
	25	2 30.70			45 1.10		Otic preparations	Ibuprofen
	28	2 30.7/			71 1.09		Amonicillin trihydrate	lbuprofen
	2/	2 11.0			38 2.90		Antibiotic combination	Sodium chloride
	20	2 21			40 15.00		Ketamine HCI Midazolam HCI	Morphine sulfate Local anesthetic combin
	<i>a</i> w	2 11.0			36 2.82		Lidocaine/epinephrine	Sodium chloride
	34	2 11.0			40 2.80		Lidocaine HCI	Sodum chloride
	30	2 7.8			75 3.78		Cettriarone sodium	Lidocaine HCI
	10	2 17.2			72 1.65		Celtriatone sodium	Acetaminophen
	34	2 46			57 6.03		Ketorolac tromethamine	Diphenhydramine
	36	2 172			56 1.62		Ketorolac bornethamine	Ondansetron HCI
	M	2 7.00			55 3.55		Midazolam HCI	Lidocaine HCI
	37	2 11.0			21 2.43		Local anesthetic combin	Sodium chloride
	38	2 7.8			40 3.38		Fentanyl	Lidocaine HCI
	39	2 7.8			50 3.34		Morphine sulfate	Lidocaine HCI
	40	2 11.0			66 236		Cettriaxone sodium	Sodium chloride
	41	2 1.97			39 12.93		Fentanyl	Midazolam HOI
	42	2 11.03	2 2	(4) 0	38 231	5822.0Ketamine HCI ==> Sodium chloride	Ketamine HCI	Sodium chloride
	43	2 43			84 5.81		Albuterol sulfate	Prednisolone
	44	2 8.0			73 3.01		Albuterol suifate	Dexamethasione
	45	2 7.00			48 1.07		Ketorolac tromethamine	Lidocaine HCI
	45	2 17.2			56 1.35		Sodium chloride	Ondansetron HCI
	47	2 1.4			40 15.00		Morphine sulfate	Ketamine HCI
	48	2 7.80			40 2.80		Sodium chloride	Lidocaine HCI
	49	2 47			71 4.47		Dexamethasone	Ipratropium bromide
	50	2 11.0			41 1.91		Midazolam HCI	Sodium chloride
	51	2 0.60			42 34.54		Ketorolac tromethamine	Prochlorperazine
	52	2 30.71			52 0.66		Cettriaxone sodium	ibuprofen
	53	2 15			30 12.03		Midazolam HCI	Fertanyl
	54	2 172			51 1.12		Lidocaine HCI	Ondansetron HCI
	55	2 17.2			40 1.10		Amonicillin trihydrate	Acetaminophen
	55	2 30.7	1	.78 0.	76 0.55	11692Local anesthetic combin === ibuprofen	Local anesthetic combin	Ibuprofen

Display 4. Table of association rules from LA

In the Results window of the Link Analysis node, select View \rightarrow Plots \rightarrow Items Constellation Plot from the main menu, it will display the link graph (Display 5), which represents associations between all drugs and visualizes drug-drug combinations. The plot provides better understanding for clinicians who want to know prescription patterns of certain medical condition. The rules data yield nodes and links data in the plot, each drug is represented by a circle called node and the association is represented by a line called edge or link. The larger the node is, the more frequently the drug had been used. The thicker the link is, the more frequently the two drugs had been used concurrently. In this example, Ibuprofen was the most commonly used drug. We found that there were 1507 two drug combinations. The top 5 most common drug combinations are listed in Table 6. One can see the detail drug combinations in the link data (Display 6).



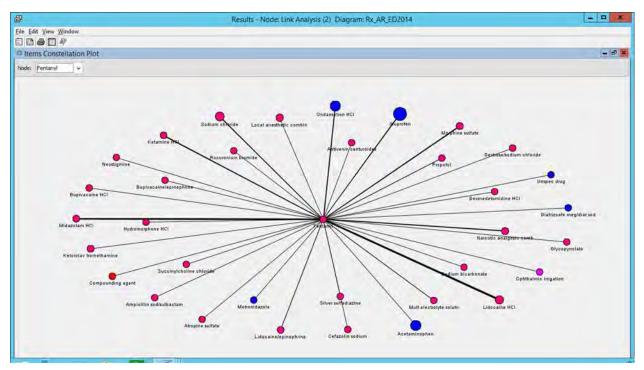
Display 5. Items Constellation Plot.

			Regults - Nod	e: Unk Analysis (2) Diagrami Ro	AR ED2014			- 0
Edit View Window			100.001.000					
								-10
tems Constellation Plot - Link	ic Data							(-)8
pecied Cashdence(%)	Contractor %	Support	LIE	Transaction Court	Left Rant of Los	Right Hand of Link	239000	
	11.36	99.12	4.73	8.73	72955 lptatropium bromide	Albuterol suitate		
	477	41.00	4,75	873	72956Albuterol suitate	lpratropium scomide		
	11,35	65.91	2.84	5.61	43769Predescione	Albutece suitale		
	431 1135	26.01	2.84	581	43769 Albuterol suitate	Prednisolone		
	8.01	34.34 24.10	273 273	301	42171Dexamethason#	Alcufesol suitate		
	30.78	16.10	2.60	0.49	42171 Autouterol autoate 40070 Oridan setton HCI	Decementatione mucrolen		
	17.21	8:44	2.60	0.49	40070 bibiprofen	Ondanselson HCI		
	17.21	8.32	2.56	0.49	39488 ibugiofen	Acetamintophen		
	30.78	14.88	2.56	0.48	39488 Acetaminophen	nelorquol		
	17.21	23.23	2.56	135	39481 Sodium miloride	Ondarsetine HCI		
	11.02	14.88	2.50	1.35	39481 Ondansetton HCI	Sodium chloride		
	17.21	14.14	2.43	0.82	37521 Ondamatron HCI	Acetaminochen		
	17.21	14.13	2.43	0.62	37521Agetaminophen	Ondanselton HCI		
	7.80	21.81	2.40	2.80	37068 Sodium chionida	Lidocaline HCI		
	11,02	30.82	2.40	2.00	37050 Liobcame HICI	Sadium chlorige		
	4.77	40,60	1,78	8.91	26952Prednisolone	lpratrapismi brömide		
	431	36.63	175	8.51	26952 lpratiopium bromide	Frechasolone		
	E.01	35.83	1.71	4.47	26372 lptatropium bromide	Delaméthasone		
	4.77	21.35	171	4.47	26372Dexameltisaone	lpksbjoplums bromide		
	30.78	14.28	1.57	0.46	24261Sodium chloride	Duprofeo		
	11.02 17.21	511 1373	157	0.46 0.80	24261 louproten	Sodium chloride		
	17.21	879	1.51	0.80	23325 Sodium chionde 23325 Acetaminophien	Acataminophen Sodium chloride		
	7.00	8.75	1.51	1.12	23325 Acetaminophen 23216 Ondansetron HCI	Lidočalok HCI		
	17.21	1931	1.51	1.12	23216Lidocaine HCI	Ondangelron HCI		
	30.78	12.77	1.45	0.42	22353 Alouterol suitate	ibupidim		
	30.78	36.29	1.27	0.53	19554LHSocaine HCI	Outroten		
	4.52	1100	121	2.43	18484Sodium chloride	Local anesthetic company		
	11.02	26.81	121	243	18684Local aneithetic combin	Solium chloride		
	2.00	10.16	1.12	5.07	17264 Sodium chloride	Ketorolac trottiethamine		
	11.02	55.91	1.12	5.07	17264Ketorolac tromethamine	Sodium chioride		
	30.78	12.81	1.03	0.42	15823Dexamelhasone	ibuprotes		
	17.21	8.93	1.01	0.52	15594-Albuterol sultate	Acetaminophen		
	11.30	5.87	1.01	0.52	15594 Apetaminophen	Alberterol suitate		
	17.21	12.13	0.95	0.70	14583Lidocame HCI	Acetaminophen		
	7.60	5.49	0.96	0.70	14583Acetammophen	Lidocaine HCI		
	11.35	8.16	0.90	0.72	13872 Sodium chloride	Albuterce suitate		
	11.02	7.93	0.90	072	13872Alboterol sulfate	Sodium chloride		
	2.17	7.57	0.83	3.49 3.40	12658 Sodium ch/odde	Morphine suitate		
	17.21	38.40	0.83	3.40 0.58	12658Morphine suitate 12284Dexamethasone	Sodium chionde Acetamenophen		
	17.21	36.43	0.60	2.12	12178Morphine pullate	Ondanselvon HDI		
	30.78	30.43	0.70	0.55	15592Local anesthetic combin	Choprofen		
	3.64	0.64	0.75	3.78	15062Local anesthesic company. 11506Lidocame HCI	Cellnaxont sodium		
	7.50	29.48	0.75	3.78	11598 Cettrakone sodkimi	Lidocaine HCI		
	17.21	28.42	3.72	185	11179Celtraxone sodium	Acetaminophen		
	8.01	83.78	0.72	7.96	11080Epineptrine	Dexamethacione		
	1.13	8.97	0.72	7.96	11050Dexamethasone	Epinephrite		
	30.78	33.57	0.71	1.02	10904 Amosicillas Britydrote	Bupplen		
	4.58	6.20	3.68	1.33	10542 Sodium chiloride	Dipheonydramine		
	11.02	14.60	3.68	1.83	10542Diphenhydramine	Socium childride		
	2.60	0.01	0.00	2.38	10209 Sodium chiloride	Cethiaxone sodium		
	11.02	25.96	0.66	2.36	10209 Cettriaxone sodium	Sodium chloride		
	17.21	42.66	9.63	2.48	2766 OKetamane HCI	Cindans etroin HCI		
	4.52	31.19	0.62	5.90	9485 0 Midazolam HCI	Local anesthetic combin		

Display 6. Link Data Screenshot

If one is interested in particular node (for example, fentanyl in this case), select the node from the Node list. Any drug of interest can be selected. Once selected, all nodes connected to the selected node you

are displayed, as shown in Display 7. The plot shows fentanyl concurrently used with 34 other drugs respectively.



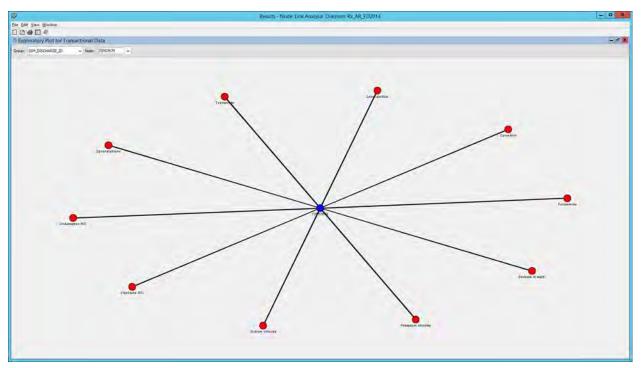
Display 7. Drug Fentanyl Concurrently Used With

We subset the link data with fentanyl involved (Display 8) and identified that three of the drug combinations (Fentanyl + Midazolam HCI, Fentanyl + Morphine sulfate, fentanyl + Hydromorphone HCI) may cause adverse drug-drug interactions and ADEs (additive respiratory depression) using DRUG-REAX® system (Thomson Micromedex®, Truven Health Analytics Inc., Greenwood Village, Co, USA) [5].

Expected		Centidence(Ta)	Support (S)	Lit	Transaction	Left Marid of Left	Right Harid of Link.	Lekito		
	1.85	5:12	0.45	1.58		Litecarry HD	Ferdanyl			
	7.82	26.37	0.40	3.56		Fartanyl	Lidoceine HCI			
	1.51	19.57	0.39	12:53		Midalidan HD	Feritaryi			
	1.57	25-61	0.38	12.51		Fentiary	Midapolan HC			
	7.27	17.00	0.26	0.99	3970.0	Fartlery!	Ondersetion HCL			
	0.78	15.43	0.23	0.50	3603.0	Fertarul	Bugerplan			
	1.02	15.87	0.23	1.25	3236.0	Fantanyl	Stidum chichder			
	1.51	8.52	0.18	5.62		Morphive suitete	Fertanyl			
	2.17	52.20	0.10	5.63		Festing	Hophese sulfate			
	1.53	19.87	34.0	7.34		Ketanine HCI	Fertany			
	1.42	11.64	0.56	7.54		Feitarel	Ketamole HCI			
	2.92	18.67	0.15	3.29		Festanul	Norcitte animpress south			
	6.52	0.28	610	1.96		FortineVL	Local anesthesic combin			
	1.53	-39-28	0.12	25/34	1835.0	Propolisi	Ferdury			
	0.90	2.86	0.12	25.54	1635.0	Fertanyi	Piopolal			
	1.5.7	7.67	2.39	5.04	1979.0	Litecarie issnephine	Fertand			
	1.12	5-8P	0.09	5.04	1272.0	Festanti	Lidbcarre. ImpringPatrie-			
	7.23	5.90	0.01	0.32	1263-0	Faritariat	Acetameteorien			
	1.51	31.44	80.0	20.76	129.10	Mult electrolyte actuant	Fairtanyl			
	0.26	5.45	9.08	25.76	12910	Factorial	Mult electrolyte adults			
	2.00	5.17	0.04	2.58	1206.0	Fertaryl	Keppenlang tephantifusion on			
	1.51	27.62	0.05	18.24	844.00	Calazile solum	Funkansk			
	1.83	6.07	0.04	4.01	567.00	Deatigae/jodkute chloride	fairtany!			
	1.5.1	82,79	2.03	41.47	508.00	Subtrykholme uhlonde	Fertand			
	1.51	17.51	0.02	11.56	503.00	Bupivecaine HO	Fentanyl			
	1.61	04.30	3 63	24.02	486.00	Glycopyrolaen	Feriliand			
	1.85	79.56	0.02	46.47	365.00	Reparation termine	Fertand			
	1.51	3.75	0.02	50.71	248.00	Teoplyment	Ferdaryl.			
	1.67	51 Sil.	0.62	7.91	233.00	Silver Adlatione	Feritary			
	1.81	0.96	0.01	6.57	155 (0)	Angoolin kod/kubactam	Ferilaryl			
	1.51	12.62	0.01	6.47		Hydromorekiewi HO	Ferdard			
	181	44.44	0.04	25.25	124.00	Eupireciane Aperephine	Tentanyi			
	141	15.45	0.01	10.96	113.00	Antonin sulfare	Fertileul			
	1.51	5.20	0.51	2.47	105.00	Metroridazow	Fertany			
	1.51	41.90	10.0	28.34	101.00	Demederative HCI	Fertanyi			
	1.61	5.76	0.01	1.54	09 00	Sodue boalcoute	Festanyi			
	1.51	5.53	3.01	1.65	91.00	Concrumiting agent	Fertiarul			
	18.1	11 64	0.00	7.69	56.00	Dateranate meg (Sat and	Fentanyl			
	1.51	5.65	0.00	3.85	63.00 Chepercience		Fundamyt	Fundament		
	1.53	-20183	0.00	12.00	50.00	Ophthaline impation	lantanyi .			
	1.5.7	87.67	2.50	53 93	49.00	Antwenin centursides	Fortunal			

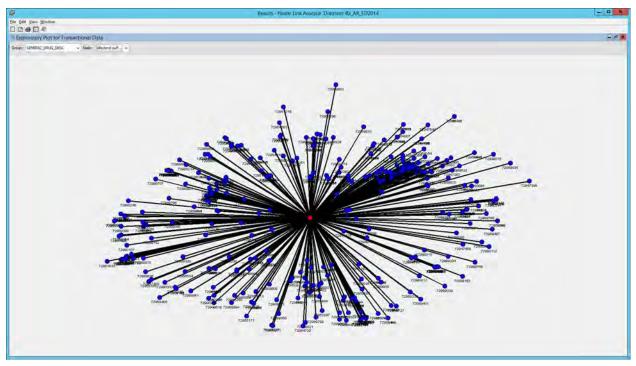
Display 8. Link Data Fentanyl

In the Results window the Link Analysis node, select View \rightarrow Plots \rightarrow Exploratory Plot from the main menu, it will display the Exploratory Plot (Display 9, Display 10) for Transactional Data to gain insight about each individual patient's drug utilization, or find each individual drug's users. For example, when one selects DIM_DISCHARGE_ID from the Group list and ID 72957679 from the Node list, one can see the various drugs that the patient took. In this example, the patient had 10 specific drugs during the ED visit (Display 9).



Display 9. Exploratory Plot for Individual Patient Drug Utilization

When one selects GENERIC_GRUG_DESC from the Group list and Albuterol Sulfate from the Node list, one sees all the individual patients who were exposed to the drug during the ED visit (Display10).



Display 10. Exploratory Plot for Individual Drug's Patient List

CONCLUSION

ARM is a powerful tool to analyze health care administrative data, and could provide additional insight into the data and detect important patterns that cannot be identified by traditional statistical methods. LA provides various graphs to visualize data. This paper shows how to use Association Node and Link Analysis Node in SAS Enterprise Miner to analyze and visualize health care administrative data. PHIS data is modified as an example of transactional data. We have shown how AMR and LA can be used to detect drug utilization and polypharmacy (drug-drug combinations) patterns and specific generic polypharmacy among sick children in emergency department visits. This application of ARM techniques has been used to analyze specific medical condition, procedure, or laboratory data associated polypharmacy in inpatient setting too (data not shown in this paper). We believe the same approach could be used in mining other databases such as administrative claims data and electronic medical records.

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