National Drug Shortage Impacts on Medi-Cal

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Drug utilization data from Medi-Cal between 2006 and 2011 were analyzed before and after the escalating shortage of sterile injectable oncology drugs (SIOs) crisis in 2009 for pattern changes in terms of the range of drug types, the prescription frequencies, the reimbursed volumes, and the drug prices. While there was no policy change in the Medi-Cal program during the study period and no decline in relevant cancer cases, the results showed statistically significant differences in the utilization patterns as well as the drug prices. Data showed a wider range of SIO drugs, on the shortage list or not, were used and the drugs were prescribed more frequently. SIO drugs not on the shortage list showed a significant increase in volume while the SIO drugs on the shortage list showed a significant price hike. This study contributes to the understanding of the demand-side impacts of drug shortages on the Medi-Cal systems.

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I. INTRODUCTION

The healthcare systems in the United States have faced a crisis in prescription drug shortages (Gatesman and Smoth 2011; Gary and Manasse 2012; Koba, 2015). The American Society of Health-System Pharmacists (ASHP) has been publishing drug shortage data since 2001. ASHP reported that from the years 2006 to 2011, the number of drug shortages increased by more than 400%, rising from 64 to 267 cases (ASHP, 2011). Drug shortages have caused many problems in patient care and increased healthcare costs for the nation. The American Hospital Association (2011) conducted a survey of hospitals nationwide and found that 99.5% of the 820 hospitals surveyed experienced some kind of drug shortage in the first six months of 2011. Kaakeh et al. (2011) estimated that annual labor cost (including pharmacists, pharmacy technicians, physicians, nurses) of dealing with the drug shortage was $216 million nationwide. The escalating drug shortage problem mandates government action. In October 2011, President Obama issued an executive order to address the issue. The government's prevention efforts have reduced the number of new cases in 2012 and 2013. Unfortunately, the number of active and ongoing shortages is still at an all-time high, with 294 and 265 active shortages in the third quarter of 2013 and the first quarter of 2015, respectively (Fox et al., 2014; Loftus, 2015).

Some researchers found that prescription drug shortage has changed patient care in the United States (Ralls et al., 2012). The New York Times reported that drug shortages are the new normal in American medicine and doctors are forced to make hard decisions on rationing treatments for patients (Fink, 2016). Many of the drugs in shortage are medically necessary for the treatment of life-threatening diseases and

have few substitutes; hence the shortage may adversely affect public health (Haninger et al., 2011; Steinbrook, 2009). When substitute medications are used to treat patients, the patients may face different side-effects and other problems such as reduced treatment efficacy. A study at St. Jude Children's Research Hospital in Memphis compared 181 Hodgkin lymphoma patients who received the preferred drug to 40 others who were given different chemotherapy and found that 15% fewer patients given the substitute drug stayed cancer-free after two years (Metzger et al., 2012). Some physicians had put off treating patients with bladder cancer or reduced the dosage due to a multi-year shortage of drug BCG (Loftus, 2015.)

II. CONCEPTUAL FRAMEWORK

Prescription drug shortage is a very complex issue in the healthcare systems in the United States. Most extant literature reviewed the shortage problem through the Medicare systems and tried to find the root causes. For example, some researchers believed that the policy change contributed to the drug shortage as the lower reimbursement decreased manufacturer's profit margins and reduced the incentive to produce some drugs (Yurokoglu et al., 2012; Federgruen, 2012; Krasomil, 2012). Payment policy by Medicare had a major change following the implementation of the Medicare Prescription Drug Improvement and Modernization Act of 2003, commonly called the Medicare Modernization Act (MMA). Before 2005, Medicare used a benchmark called average wholesale price (AWP) to reimburse doctors. Back then the AWP was an unrealistically high price quoted by drug makers, not related to the actual transaction prices. In 1998, Medicare set the reimbursement rate at 95 percent of the AWP and reduced it to 85 percent of the AWP in 2004. The benchmark that Medicare uses after MMA is called the average sales price (ASP), which is the average of actual net sales. Medicare reimbursement to healthcare providers is 106 percent of the ASP. In 2005, a survey of over 2,000 drug codes, found that that the ASP is 49% less than the AWP (Graham 2012). Yurokoglu et al. (2012) used theoretical models showing that the reimbursement benchmark change from AWP to ASP could have contributed to drug shortages.

Some researchers used surveys from targeted groups, such as pharmacy directors and oncologists, or used case studies, to determine the effect of drug shortages on patient outcomes, clinical and pharmacy operations, and institutional cost and time (Kaakeh, et al., 2011; McLaughlin, et al., 2013; Goginenni et al., 2013) or to determine the possible reasons of the shortages such as supplier issues, manufacturing process and quality, and lean inventory policy (Fox, et al., 2014; Gu, et al., 2013; Ventola, 2011).

This study, however, focuses on the investigation of the macro impacts of a category of drugs in a system that has been overlooked in previous studies—the Medicaid programs. Contrary to the Medicare program, Medicaid had no policy change on drug reimbursement prices in 2005. Medicaid prescription drug reimbursement policy remained at AWP minus 17% (Medicaid.gov 2012). The Medicaid drug reimbursement policy changed to ASP plus 6% in the third quarter of 2012. While Medicare serves mostly elderly people, Medicaid serves low-income or underprivileged people, including children and young adults. According to The National Data Book from the U.S. Census Bureau, 55.5 million people were enrolled in Medicare while nearly 72 million people were enrolled in Medicaid in 2015. If prescription drug shortages affect the systems, it may have substantial and long-term impacts on Medicaid systems as enrollment increases, especially among young people. Over three-quarters of all

Medicaid beneficiaries are children and non-disabled adults with low income.

Some drugs are more susceptible to shortage than others. Sterile injectable drugs, which are shipped in liquid or powder form for later injection into a patient, show a substantial susceptibility to the shortage. All injectable drugs are classified under the Medicare Part B program. In 2010, 74% of the FDA reported shortage drugs were sterile injectable (Lowes, 2011; GAO 2011). Of the sterile injectable drugs, the oncology group is most critical, as standard treatment regimens for many cancers have been directly compromised by shortages of these drugs (Krasomil, 2012; Link et al., 2012). A survey indicated that 82.7% of 214 randomly selected U.S. oncologists were unable to prescribe the preferred chemotherapy agent at least once between September 2012 and March 2013 because of shortages (Gogineni et al., 2013). 76.7% of the surveyed oncologists were forced to switch drugs during the treatment plan and over one-third of oncologists either delayed treatment on patients or excluded some patients from treatment. Not only do drug substitutes suffer from efficacy problems, but alternative drugs are extremely expensive, with an average markup of 650% (Cherici et al., 2011). Chen's study (2103) showed a dramatic increase in the price of sterile injectable oncology (SIO) shortage drugs after the crisis occurred. Because of these pressing circumstances, this study focused on the shortage of sterile injectable oncology drugs.

Analyses were conducted on the drug utilization data from the Medicare program in California (Medi-Cal) from 2006 to 2011, focusing on the most critical shortage category—SIO drugs. According to a report from the U.S. Department of Health and Human Services, the shortage of sterile injectable drugs escalated in 2009 with 87.5% more drugs in a shortage than 2008, and another increase of 76% in 2010 (Haninger, Jessup, and Koehler 2011). Hence this project identified the first quarter of 2009 as the cutoff point for the SIO drug shortage crisis. Quarterly SIO drug prices and utilization measures were compared before and after the crisis.

As mentioned above, Medi-Cal had no policy change on drug reimbursement prices until 2012. If the policy change on drug reimbursement pricing was associated with drug shortages and the consequences, a system such as Medi-Cal with a stable pricing reimbursement policy and a large patient base would not expect to encounter the same problems. Hence, the drug utilization patterns and the drug price in Medi-Cal should not be significantly different before and after the drug shortage crisis as in the Medicare systems. To assess the drug shortage impacts on the Medi-Cal systems, the following hypotheses were developed and tested for the SIO drugs that are on the FDA shortage list and also for the SIO drugs not on the shortage list.

Hypothesis 1: The utilization patterns of SIO drugs in Medi-Cal (as measured by drug diversity, prescription frequency, and reimbursement volume) do not differ before and after the national drug shortage crisis.

Hypothesis 2: The prices of the SIO drugs in Medi-Cal (as measured by reimbursement amount per unit) do not differ before and after the national drug shortage crisis.

III. METHODS

3.1. Data Sources

The data used in this study were mined, cleaned, verified, and integrated from various public datasets. National Drug Code

(NDC) was used as the master key to integrating data from all databases. First, the FDA drug shortage lists were reviewed to extract the NDC of all drugs in shortage, and then I identified the drugs in the SIO category. SIO drugs are grouped under the Healthcare Common Procedure Coding System (HCPCS) code J9000-J9999 range (Haninger, Jessup, and Koehler 2011). To find SIO drugs, the January 2013 NDC-HCPCS Crosswalk from the Center for Medicare and Medicaid Services (CMS) was used. Data on the Crosswalk include the HCPCS code, short description, labeler/manufacturer name, NDC or alternate code, drug name, HCPCS dosage, package size, and billable units, etc. The NDC codes from the FDA shortage list identify the shortage SIO drugs as well as non-shortage SIO drugs from Medi-Cal data.

The NDCs of the SIO drugs were used to retrieve a subset of data from the Medi-Cal Drug Utilization Database. On January 1, 2006, Medi-Cal drug coverage for individuals eligible for Medicare and Medicaid was shifted to Medicare as a result of the Medicare Modernization Act. The drug utilization database was revised subsequently. To test the hypotheses, this study analyzed data under the new policy from 2006 to 2011. Medi-Cal drug utilization data included the NDC, the period covered, FDA drug listed name, number of prescriptions, units reimbursed, total dollar amount reimbursed, Medicaid amount reimbursed, and the non-Medicaid amount reimbursed for each utilized drug on a quarterly basis.

HCPCS identified 364 SIO drugs, but 27 of them were not listed on FDA national drug directory. Out of the 337 SIO drugs found in the directory, 32 SIO drugs were on the FDA drug shortage list. A total of 376,101 Medi-Cal drug utilization records from 2006 to 2011 were analyzed, and 3,511 of them were SIO drugs; among them, 339 records belonged to the shortage SIO drugs.

To determine if the demand for SIO drugs changed over the study period, data from the California Cancer Registry were reviewed. This Registry has provided annual reports regarding the numbers of new cancer cases and mortality in fifty-three cancers since 1988. Among them, thirteen cancers are potentially treatable with SIO drugs, including lung and bronchus cancer, invasive breast cancer, various leukemia cancers, non-Hodgkin lymphoma cancers. One cancer, Kaposi Sarcoma, was excluded due to missing data after 2009.

3.2. Measures and Statistical Analysis

Each Medi-Cal drug utilization record has an NDC that represents a specific drug. To investigate the impact of the national drug shortage crisis in terms of drug utilization in Medi-Cal, three measures were used. First, the total number of unique records (referred to as record count) represented the total number of drug types each quarter. Second, the number of prescriptions per drug represented the frequency that the drug was ordered for cancer patients. Third, the reimbursed units represented the volume of the drug utilized.

To investigate the impacts of the national drug shortage crisis in terms of drug price in Medi-Cal, I estimated the drug price by dividing the total reimbursement dollar amount by the total units reimbursed for each individual drug. Since new branded drugs were often more expensive, to get a clear picture of the price changes, data used in analyzing prices were on SIO drugs introduced to the market before 2006. Drugs with extremely high reimbursement dollar amounts were considered outliers for statistical analysis. Eight outliers--seven outliers for non-shortage SIO drugs and one outlier for shortage SIO drugs were identified and removed. For the shortage SIO drugs, one outlier was in Q3 of 2011. For non-

shortage SIO drugs, three outliers were in Q3 of 2011 and four outliers were in Q4 of 2011. These outliers had a unit price over $35,000.

The scatterplots of the data showed skewed distributions and the data failed the Shapiro-Wilk normality test so the independent t-test is not appropriate. Hence, the non-parametric Mann-Whitney U test and Wilcoxon W test were used to test hypotheses. Similar to the independent t-test, the non-parametric tests determine if there is a difference between two populations at a statistically significant level to reject the null hypothesis. However, the non-parametric tests are based on data ranks and do not rely on the assumptions on the normality of the data of the two populations.

IV. RESULTS

4.1. SIO drugs Effective Cancer Cases

Some argued that the decreasing demand for SIO drugs leads to a shortage of drug supply. For example, Haninger, Jessup, and Koehler (2011) stated in a government report that "On average, drugs that subsequently experienced a shortage were those in which the volume of sales was declining in the 2006-2007 period prior to the shortages." Their study implied that the decrease in demand caused the drug manufacturer to reduce supply or even to discontinue the manufacturing of the drugs.

To ensure that the observed effect was not caused by the change in cancer growth rates, an analysis of California Cancer Registry records from 2006 to 2011 was performed. The new cases of the twelve cancers that are potentially treatable with SIO drugs ranged from 55,105 cases per year to 61,135 per year with an average of 59,085 cases per year, and the mortality rates ranged from 25,376 deaths per year to 25,868 deaths per year with an average of 25,578 deaths per year. The annual growth rate was at approximately the same level of 33,507 cases from 2006 to 2011.

Fig. 1 shows the number of cancer cases in California, in which the SIO drugs in this study are commonly used for treatment. Simple regression analysis was carried out to see if there is an upward or downward trend in growth. The result shows an insignificant trend ($p=0.381$) in the growth of the SIO effective cancer cases from 2006 and 2011. (The slope coefficient for the regression is -504.171, and the R^2 value is 0.195.) The data showed the stability of the cancer cases and hence the demand for the SIO drugs from 2006 to 2011.

4.2. New SIO Drugs

Previous studies found that shortages more greatly affect the existing generic drugs. For example, Ventola (2011) suggested that newly introduced drugs are more prone to shortage because of the complications that come with new drug introduction into a market. To identify if SIO drugs were newly introduced during this study period, I used the drug introduction dates on FDA National Drug Code Directory. SIO drugs introduced to the market before 2006 were considered existing established drugs. SIO drugs introduced to the market after 2006 were considered new drugs. Table 1 provides the breakdown of the number of SIO drugs by the drug introduction year and shortage status. The data showed that 174 SIO drugs were introduced before 2006 and 21 (12.07%) of them were on the shortage list. 163 SIO drugs were introduced after 2006 and 11 (6.75%) of them were on the shortage list. Hence the newly introduced SIO drugs are not a major part of the shortage drugs in Medi-Cal. On the contrary, the established SIO drugs were more likely to be in shortage.

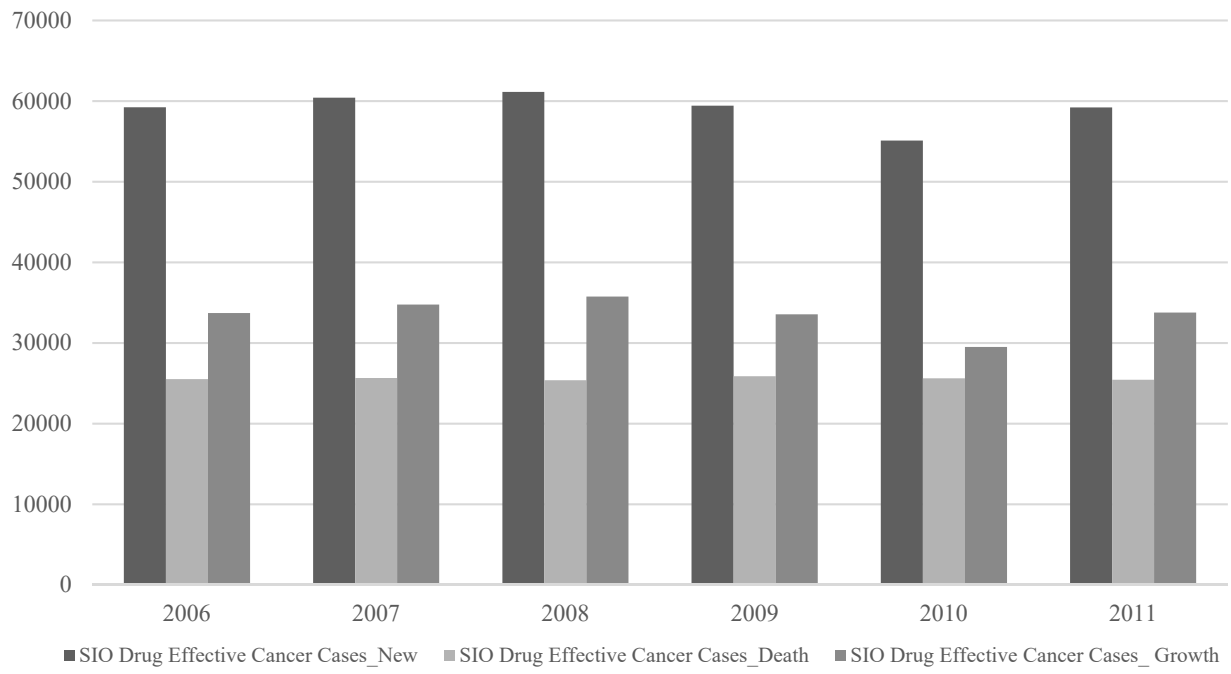

FIGURE 1. SIO DRUG EFFECTIVE CANCER CASES IN CALIFORNIA

TABLE 1. DRUG INTRODUCTION YEAR AND DRUGS IN SHORTAGE

Drug Introduction Year	# of Introduced SIO Drugs not on the Shortage list	# of Introduced SIO Drugs on the Shortage list	Total # of SIO Drugs Introduced
Before 2006	153	21	174
2006	17	0	17
2007	14	1	15
2008	16	1	17
2009	30	6	36
2010	20	0	20
2011	55	3	58

4.3. Utilization Patterns and Prices

The non-parametric Mann-Whitney U test and Wilcoxon W Test were conducted to see if the changes in drug utilization and prices were statistically significant. Table 2 shows the test results. For Hypothesis 1 on drug utilization for shortage SIO drugs, the non-parametric tests rejected the null hypothesis in terms of the drug count and the number of prescriptions, but not on the reimbursed units. The data showed that 73.48% more types of SIO drugs were in shortage after the national drug shortage crisis. Interestingly, physicians issued 60.52% more prescriptions on the SIO drugs in shortage. The reimbursed volume of the SIO drugs in shortage was also increased by 20%, but the increase was not significant. For Hypothesis 1 on drug utilization for non-shortage SIO drugs, the non-parametric tests rejected the null hypothesis in all three measures. For non-shortage SIO drugs, further analyses showed that after crisis 166.27% more types of SIO drugs were utilized in the Medi-Cal program, 141.99% more prescriptions of those drugs were issued by the physicians, and the reimbursed volume was 347.99% more after the crisis. Much of the increase in the range of drug types started in 2010 while the increase of volume and prescriptions started in 2009.

For Hypothesis 2, the non-parametric Mann-Whitney U and Wilcoxon W tests found a significant change in drug prices for shortage SIO drugs, but not for non-shortage SIO drugs. Data used in this analysis were on established SIOs introduced to the market before 2006 so the prices were expected to be stable. Reviewing the data, the average price of established SIO drugs in shortage showed a significant increase after the national drug shortage crisis. The average price of established SIO drugs in shortage was $33.59 before the crisis and $84.98 after the crisis, an increase of 153%. On the contrary, the average price of the established SIO drugs not in shortage was $436.94 before the crisis and $475.71 after the crisis, an increase of only 8.87%.

The SIO drug category had strong growth in comparison to all drug groups in the Medi-Cal program from 2006 to 2011. In fact, the number of all drug types in the Medi-Cal program was decreased by 6.07% after 2009 and the reimbursed volume of all drugs was decreased by 14.48% after 2009.

Fig. 2 shows a surge in the frequency and volume of non-shortage SIO drugs after the national drug shortage crisis. On average the number of prescriptions per non-shortage SIO drug was 38.2 per quarter from 2006 to 2008 and 92.6 per quarter from 2009 to 2011. In contrast, the average number of prescriptions per shortage SIO drug was 35.1 per quarter from 2006 to 2008 and 56.3 per quarter from 2009 to 2011. The average reimbursed units per non-shortage SIO drug was 927.12 per quarter from 2006 to 2008 and 4153.38 per quarter from 2009 to 2011. In contrast, the average reimbursed units per shortage SIO drug was 257.53 per quarter from 2006 to 2008 and 309.07 per quarter from 2009 to 2011.

It was interesting to see that the drug shortage crisis generated an increase in the overall SIO drug usage in the Medi-Cal program. In response to the national shortage crisis on SIO drugs, physicians explored and prescribed various types of SIO drugs. It was also interesting to notice that more new drugs were introduced to the market after 2009. Table 3 shows further analysis using regressions. The results showed a significant upward trend with new SIO drugs introduced at a rate of 6.55 drugs per quarter since 2009. Pre-2009 the regression analysis showed a significant downward trend for new SIO drugs at a rate of 0.32 decrease per quarter.

Fig. 3 shows the average price of shortage SIO drugs and non-shortage SIO drugs per quarter from 2006 to 2011. The

time series plots demonstrated that established shortage SIO drugs' average prices were much less expensive compared to the average prices of established non-shortage SIO drugs. On the other hand, for newer SIO drugs that were on the shortage list, the prices were as expensive as the price of the SIO drugs not on the shortage list. An upward trend of the average prices was observed on the established shortage SIO drugs but not on the established non-shortage SIO drugs.

TABLE 2: NON-PARAMETRIC TESTS ON HYPOTHESES

			N	Mean	Std. Dev.	Mean Rank	Mann-Whitney U Test	Wilcoxon W Test	Z	Asymp. Sig (2-taled)
Shortage SIO Drugs	Drug Count	Before crisis	12	10.33	1.23	9.50	36.000	114.000	-2.097	***0.036***
		After crisis	12	17.92	7.83	15.50				
	Number of Prescription	Before crisis	12	35.08	7.66	7.46	11.500	89.500	-3.494	***0.000***
		After crisis	12	56.31	14.87	17.54				
	Reimbursed Units	Before crisis	12	257.53	93.04	9.92	41.000	119.000	-1.790	0.073
		After crisis	12	309.07	77.46	15.08				
	Reimbursed Drug Price	Before crisis	12	$33.59	$11.58	8.17	20.000	98.000	-3.002	***0.003***
		After crisis	12	$84.98	$47.71	16.83				
Non-Shortage SIO Drugs	Drug Count	Before crisis	12	72.17	5.86	8.42	23.000	101.000	-2.830	***0.005***
		After crisis	12	192.17	84.84	16.58				
	Number of Prescription	Before crisis	12	38.25	9.87	7.25	9.000	87.000	-3.637	***0.000***
		After crisis	12	92.56	41.77	17.75				
	Reimbursed Units	Before crisis	12	927.12	245.11	6.92	5.000	83.000	-3.868	***0.000***
		After crisis	12	4153.38	2524.52	18.08				
	Reimbursed Drug Price	Before crisis	12	$436.94	$190.03	10.17	44.000	122.000	-1.617	0.106
		After crisis	12	$475.71	$181.80	14.83				

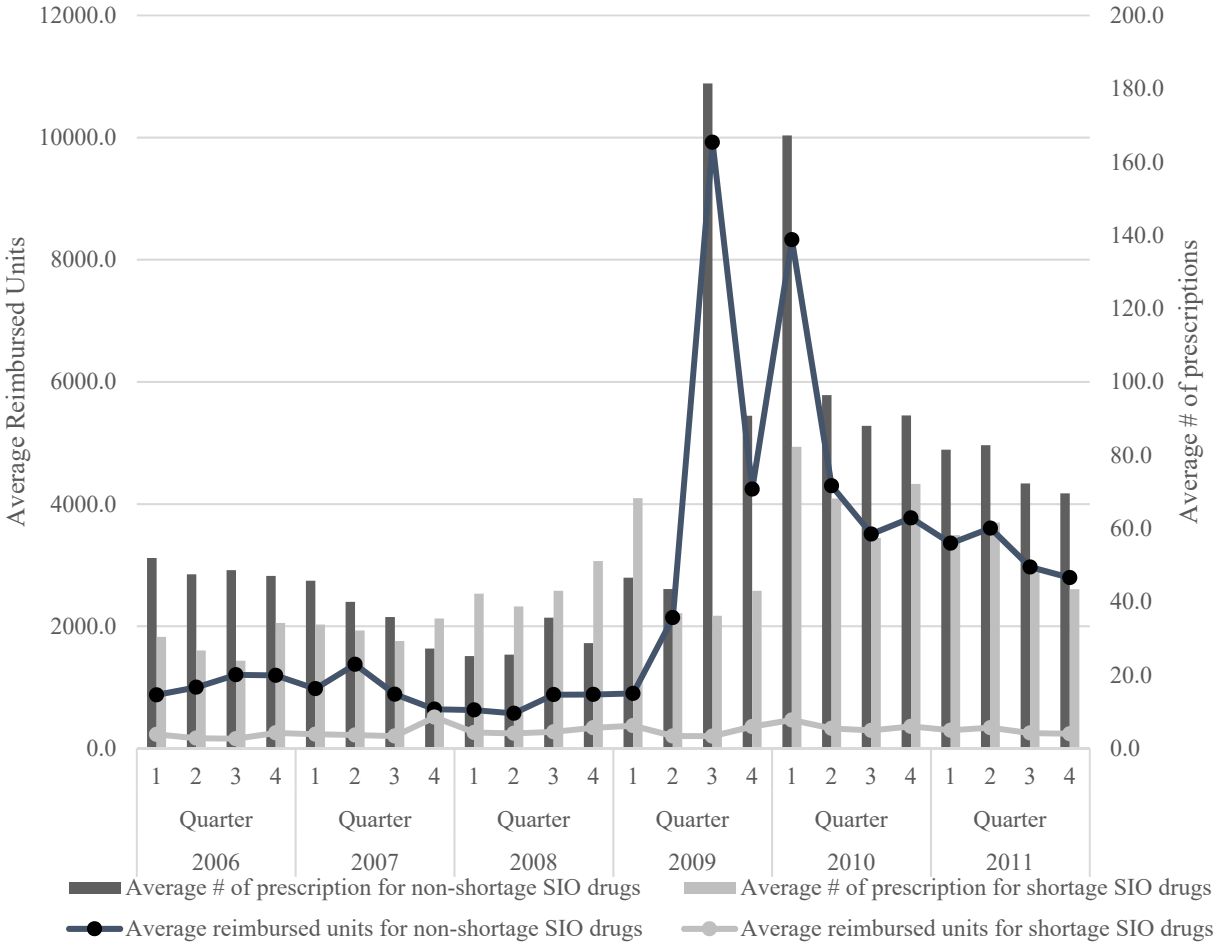

FIGURE 2: AVERAGE REIMBURSED UNITS AND THE NUMBER OF PRESCRIPTIONS OF SIO DRUGS IN MEDI-CAL, 2006-2011

TABLE 3: REGRESSION RESULTS FOR THE NUMBER OF NEW SIO DRUGS BEFORE AND AFTER THE DRUG SHORTAGE CRISIS

	Before Crisis	After Crisis
Constant	10.091 (0.348)	-1.924 (4.618)
Time (in quarters)	-0.322*** (0.047)	6.552*** (0.627)
Multiple R	0.907	0.957
R-squared	0.822	0.916
Adjusted R-squared	0.804	0.908
No. observations	12	12

Standard errors in parentheses. *** $p < 0.000$

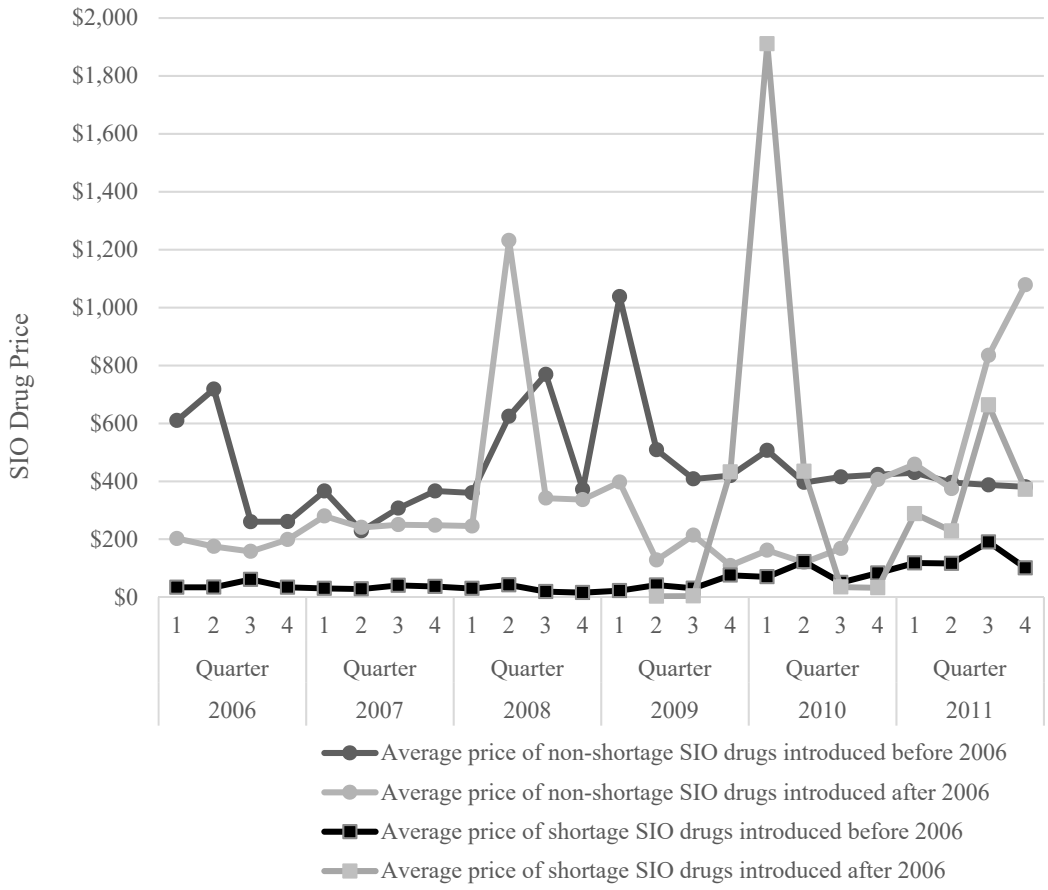

FIGURE 3: AVERAGE REIMBURSED PRICE OF SIO DRUGS IN MEDI-CAL, 2006-2011

V. DISCUSSION

In the literature reviewed, one of the frequently proposed associations of the drug shortage was the policy change of the Medicare system that brought about substantial changes in drug prices. Researchers suggested that the lower mandated prices decreased the profit for drug manufacturers. Instead of producing low-margin drugs, drug manufacturers would switch to the production of higher-margin drugs (Fox et al. 2009; Cherici et al. 2011). Medi-Cal system did not have the reimbursement policy change during the time of the study. However, the study results clearly showed significant drug utilization patterns and price changes. If the Medicare policy change was one of the reasons for the national drug crisis, this study showed the spillover effects in the Medi-Cal program where there was no policy change on drug reimbursement. Since Medicare and Medi-Cal are subsets of the overall healthcare industry in the United States, the policy change in one market affected prescription drug utilization in another market, causing changes in effective demand patterns.

This study showed strong growth of the SIO drugs post the crisis, a wider range of drugs was used and more prescriptions were issued. This can be explained by the substitution effect and income effect in economics. Studies on physician's responses to Medicare payment cut found similar effects (Jacobson and Newhouse, 2010; Jacobson, et al., 2010). They found that a fee cut for one service made other services more attractive—a substitution effect. Physicians may be forced to use alternative drugs, which are typically the more expensive branded or new drugs (Kreling 2000). For example, the American Hospital Association (2011) found that 92% of the 820 hospitals surveyed purchased more expensive alternative medicine or turned to alternative sources. A survey by McLaughlin et al. (2013) found 85.3% of the 193 directors of pharmacy reported using alternative medication due to drug shortages. Jacobson and Newhouse (2010) also found that fee cut for service(s) led to more usage of the service(s) to make up to some of the lost income—an income effect. In this study, SIO drugs are critical to cancer patient treatments. The drugs in shortage were effective and less expensive ones. Facing shortage possibilities, physicians prescribed them more frequently in an effort to claim the remaining supply/inventory (i.e. income) to preserve patient treatment plans.

The average price of the non-shortage established SIO drugs was 12 times more expensive than the average price of the established shortage SIO drugs before the crisis. Since the crisis in 2009, the gap was narrowed to 4.6 times due to the 153% price hike of the established shortage SIO drugs. The price of the new non-shortage SIO drugs introduced after 2006 was on average 14% lower than the price of the established non-shortage SIO drugs. However, the price of the new and in–shortage SIO drugs was 6.75 times more expensive than the average price of established SIO drugs in shortage. In other words, the price hike happened to established and new SIO drugs when they were in shortage.

VI. LIMITATIONS AND FUTURE STUDIES

This study has several limitations. Although Medi-Cal is the largest Medicaid program in the United States, accounting for 17.21% of the total Medicaid enrollment, there are forty-nine other states with Medicaid programs. The findings of this study may not be generalized to other programs. For example, Maine and Vermont may have a smaller impact on per-capita drug usage (IMS Institute for Healthcare Informatics 2011). The study used aggregated quarterly drug utilization data so the findings do not necessarily apply to individual drugs. Further, the drug utilization data includes the fee-for-service outpatient drugs reimbursed by Medi-Cal to pharmacies but does not include inpatient drug data. This study relied on the accuracy and availability of the data published by the California Department of Health Care Services.

This study conducted analyses more on the demand-side of factors in the government-managed healthcare sector. I focused on drug shortage impact to cost and utilization patterns. Analysis of data from private insurers would help compare and verify trends observed in the government systems. Researchers could also examine the efficacy and side effects of alternative drugs to see the impact on patient treatments.

Further studies shall investigate the supply-side of factors. For example, the operational performances, such as raw materials and finished good inventory levels and gross margins, of the manufacturers that produce the drugs in shortage could be analyzed to develop better inventory policies and monitor the bullwhip effect. Supplier

networks could be mapped out to find vulnerable links to make the supply chains more resilient. The complexity of the drug shortage issues cannot be fully understood unless the supply-side of factors are evaluated and addressed together.

VII. CONCLUSION

This study contributes to the understanding of the multifaceted prescription drug shortage challenge in the United States. The SIO drug utilization data in the Medi-Cal program, which was overlooked in the literature, were investigated to provide a macro-level evaluation of the demand-side impact of the crisis. While there was no policy change in the Medi-Cal program during the study period and no decline in relevant cancer cases, the results showed the spillover effects from the Medicare system. Data showed a wider range of SIO drugs, on the shortage list or not, were used and the drugs were prescribed more frequently. SIO drugs not on the shortage list showed a significant increase in volume while the SIO drugs on the shortage list showed a significant price hike. The drug shortage issue in the Medicare system has affected the drug treatment options for cancer patients and the drug reimbursement costs in the Medi-Cal program.

The healthcare industry is an integrated market for medicine. Changes in one part of the market may affect other parts of the market. Healthcare policymakers and decision-makers should be cautious in the impact of any future policy changes and be prepared for the spillover effect, substitution effect, and income effect, as demonstrated in this study.

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REFERENCES

American Hospital Association. *AHA Survey on Drug Shortages*. July 12, 2011, http://www.aha.org/content/11/drugshortagesurvey.pdf (accessed January 15, 2013).

ASHP (American Society of Health-System Pharmacists). *Drug Shortages: Current Drugs*, 2011, http://www.ashp.org/menu/DrugShortages/CurrentShortages (accessed December 15, 2012).

California Department of Public Health (CDPH). *California Cancer Registry. Cancer Surveillance Section,* http://www.ccrcal.org (accessed January 7, 2013).

Chen, E. "An Analysis of Sterile Injectable Oncology Drug Shortages in the California Medicaid Program", Interactive Poster Session, *INFORMS Healthcare Analytics Conference*, June 23-26, 2013, Chicago, IL.

Cherici, C., Frazier, J., Feldman, M., Gordon, B., Petrykiw, C., Russell, W., and J. Souza. *Drug Shortages in American Healthcare*. Premier Healthcare Alliance, 2011, https://www.premierinc.com/about/news/11-mar/drug-shortage-white-paper-3-28-11.pdf. (accessed January 15, 2013).

Cherici, C., McGinnis, P., and Russell, W., *Buyer Beware: Drug Shortages and the Gray Market.* Premier Healthcare Alliance, 2011, https://www.premierinc.com/about/news/11-aug/Gray-Market/Gray-Market-Analysis-08152011.pdf (accessed March 15, 2013).

Federgruen, A., "The Drug Shortage Debacle-and How to Fix It", *The Wall Street Journal.* March 1, 2012.

Fink, S., "Drug Shortages Forcing Hard Decisions on Rationing Treatments", *The New York Times*, January 29, 2016.

Fox, E., Sweet, B.V., and Jensen, V., "Drug Shortages: A Complex Health Care Crisis", *Mayo Clinic Proceedings* 89, 3, 2014, 361-373.

Fox, E.R., Birt, A., James, K.B., Kokko, H., Salverson, S., and Soflin, D. L. "ASHP Guidelines on Managing Drug Product Shortages in Hospitals and Health Systems", *American Journal of Health-System Pharmacy,* 66, 15, 2009, 1399-406.

GAO. *Drugs Shortage: FDA's Ability to Respond Should Be Strengthened*. Report to Congressional Requesters, U.S. Government Accountability Office, Washington, .D.C. November 2011, http://www.gao.gov/assets/590/587000.pdf (accessed December 15, 2012).

Gatesman, M. L., and T. J. Smith, "The Shortage of Essential Chemotherapy Drugs in the United States", *The New England Journal of Medicine,* 365, 18, 2011, 1653-5.

Gray, A. and Manasse, H. R., "Shortages of Medicines: a Complex Global Challenge", *Bull World Health Organ,* 90, 3, 2012, 158-58A.

Graham, J., "The Shortage of Generic Sterile Injectable Drugs: Diagnosis and Solution", *Policy Brief, Mackinac Center for Public Policy*, June 14, 2012.

Gogineni, K., Shuman, K. L., and Emanuel, E. J., "Survey of Oncologists about Shortages of Cancer Drugs", *The New England Journal of Medicine,* 269, 25, 2013, 2463-2464.

Gu, A., Wertheimer, A., Brown, B., and Shaya, F., "Drug Shortages in the US-Causes, Impact, and Strategies", *INNOVATIONS in Pharmacy*, 4, 60, 2011, 1-8.

Haninger, K., Jessup, A., and Koehler, K. (2011). *Economic Analysis of the Causes of Drug Shortages.* Assistant Secretary for Planning and Evaluation (ASPE) Issue Brief, 2011, http://aspe.hhs.gov/sp/reports/2011/drugshortages/ib.pdf (accessed February 10, 2013).

IMS Institute for Healthcare Informatics Report. *Drug Shortages: A Closer Look at Products, Suppliers, and Volume Volatility. November 2011,* http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Static%20Files/IIHI_Drug_Shortage_Media_ExecSumm.pdf (accessed December 15, 2012).

Institute for Safe Medication Practices (ISMP), *Gray Market, Black Heart: Pharmaceutical Gray Market Finds a Disturbing Niche during the Drug Shortage Crisis,* August 25, 2011, http://www.ismp.org/Newsletters/acutecare/showarticle.aspx?id=3 (accessed July 15, 2014).

Jacobson, M. and Newhouse, J. P. *Expect the Unexpected? Physicians' Responses to Payment Changes*, National Institute for Health Care Management, November 2010, http://www.nihcm.org/pdf/EV-JacobsonNewhouseFINAL.pdf (accessed September 11, 2015).

Jacobson, M., Earle, C. C., Price, M., and Newhouse, J. P., "How Medicare's Payments Cuts for Cancer Chemotherapy Drugs Changed Patterns of Treatment", *Health Affairs*, 29 (7), 2010, 1394-1402.

Kaakeh, R., Sweet, B. V., Reilly, C., Bush, C., DeLoach, S., Higgins, B., Clark, A. M., and Stevenson, J., "Impact of Drug Shortages on U.S. Health Systems", *American Journal of Health-System Pharmacy*, 68, 19, 2011, 1811-9.

Koba, M., "The U.S. Has a Drug Shortage- and People Are Dying", *Fortune*, January 6, 2015, http://fortune.com/2015/01/06/the-u-s-has-a-drug-shortage-and-people-are-dying/ (accessed October 2, 2016).

Krasomil, E. A., *Measuring the Impact of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 on Shortages of Sterile Injectable Oncology Drugs*, Master thesis, Sanford School of Public Policy, Duke University, 2012.

Kreling, D. H., *Cost Control for Prescription Drug Programs: Pharmacy Benefit Manager PBM Efforts, Effects, and Implications.* A background report prepared for the Department of Health and Human Services' Conference on Pharmaceutical Pricing Practices, Utilization, and Costs, Washington, DC. August 8-9, 2000, http://aspe.hhs.gov/health/reports/drug-papers/kreling-final.htm (accessed July 14, 2014).

Link, M. P., Hagerty, K., and Kantarjian, H. M., "Chemotherapy Drug Shortages in the United States: Genesis and Potential Solutions", *Journal of Clinical Oncology,* 30, 7, 2012, 692-4

Loftus, P., U.S. "Drug Shortages Frustrate Doctors, Patients", *The Wall Street Journal*, May 31, 2015. http://www.wsj.com/articles/u-s-drug-shortages-frustrate-doctors-patients-1433125793 (accessed August 30, 2016).

Lowes, R., *Sterile Injectables Account for Most of Drug Shortage.* September 30, 2011, http://www.medscape.com/viewarticle/750790 (accessed December 15, 2012).

Medicaid.gov., *Medicaid Covered Outpatient Prescription Drug Reimbursement Information by State,* 2014, http://medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Downloads/StateReimbChart2Q2012.pdf (accessed July 15, 2014).

McLaughlin, M., Kotis, D., Thomson, K., Harrison, M., Fennessy, G., Postelnick, M. & Scheetz, M., "Effects on Patient Care Caused by Drug Shortages: A Survey", *Journal of Managed Care Pharmacy*, 19, 9, 2013, 783-8.

Metzger, M. L., Billett, A. & Link, M. P., "The Impact of Drug Shortages on Children with Cancer--the Example of Mechlorethamine", *The New England Journal of Medicine*, 367, 26, 2012, 2461-3.

Ralls, M. W., Blackwood, R. A., Arnold, M. A., Partipilo, M. L., Dimond, J. Teitelbaum, D. H., Drug "Shortage-Associated Increase in Catheter-related Blood Stream Infection in Children", *Pediatrics*, 130, 5, 2012, e1369-73.

Steinbrook, R., "Drug Shortage and Public Health", *The New England Journal of Medicine,* 361, 6, 2009, 1525-7.

Travernise, S., "Shortages Continue to Vex Doctors", *The New York Times*, Feb. 11, 2014, A15.

Ventola, C. L., The Drug Shortage Crisis in the United States: Causes, Impact, and Management Strategies. *Pharmacy and Therapeutics*, 36, 11, 2011, 740-757.

Yurokoglu, A., Liebman, E., Ridley, and D. B., *Medicare Reimbursements and Shortages of Sterile Injectable Pharmaceuticals.* Graduate School of Business, Stanford University, and NBER, 2012, http://web.stanford.edu/~ayurukog/shortages.pdf (accessed December 15, 2012).