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Impact Of Refill Synchronization On Medication Adherence For Chronic Diseases

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IMPACT OF REFILL SYNCHRONIZATION ON MEDICATION ADHERENCE FOR CHRONIC DISEASES

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By

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ABSRACT

Objectives: The objective of this study is to assess the impact of medication synchronization (med sync) on medication adherence for three drug classes under the CMS Star Rating system i.e. oral diabetes, hypertension and cholesterol.

Methods: A quasi-experimental pre-post study design was employed using pharmacy prescription fill data from various independent community pharmacies located in different regions of Mississippi. Using Proportion of Days Covered (PDC), medication adherence before and after the med sync was calculated. Total study period of one year for each patient including six months of pre-period and post-period was used for the analysis. Descriptive statistics were calculated. Wilcoxon-Signed Rank test was performed to compare the pre-period adherence to post-period adherence. Proportion of adherent patients before and after the med sync were also compared using McNemar's Exact Test. Using the obtained 2x2 contingency table odds ratio of being adherent in post-period as compared to pre-period was calculated.

Results: A total of 56, 89 and 77 patients were found to meet the inclusion/exclusion criteria in diabetes, hypertension and cholesterol drug categories, respectively. The approximate average age of the patients for the three drug classes was as follows: diabetes 66 years (23-87 years, ± 11.03), hypertension: 70 years (41-101 years, ± 11.53) and cholesterol: 67 years (40-100 years, ± 11.85). Majority of the study sample belonged to 60-80 years of age and had PDC values ranging from 90-100 in both pre-period and post-period for all the three drug classes. Average post-period PDC (0.99) was higher than average pre-period PDC (0.94) and was also

statistically different from each other for all the three drug classes. Increase in the proportion of adherent patients from pre-period to post-period was witnessed for the three drug classes i.e., diabetes (91.07% to 100%), hypertension (89.89% to 98.88%) and cholesterol (90.91% to 98.70%). However this increase was only statistically significant for the hypertension drug class (*p=0.0215*). Also, patients in post-period had higher odds of being adherent in post-period as compared to pre-period for all the three drug classes.

Conclusions: The results indicated that after being enrolled in med sync, medication adherence generally improves.

DEDICATION

This thesis is dedicated to my Chaiji, Papaji, parents and fiancé, for all their blessings and support; and especially for believing that I could do it.

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Divya Verma

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CHAPTER I

INTRODUCTION

The problem of non-adherence

Medication non-adherence, or the failure to take medications as prescribed, is one of the most significant factors limiting the effectiveness of medications in practice.[1] Almost two-thirds of Americans are non-adherent to medications[2] and specifically, 50% of patients taking chronic medications are non-adherent.[1] Hospitalizations, morbidity and mortality are some of the consequences associated with medication non-adherence.

The causes of non-adherence are dynamic and varies by individual. Non-adherence can be related to age, culture, social background, values, and attitudes. Disease-related factors such side effects of the medication, treatment duration, frequency of expected intake, and treatment complexity also impacts patients' medication taking behaviors. Some external factors contributing to non-adherence are the relationship between the patient and the physician or the nurse, support from the family, health care personnel, and friends and also the amount of health education a patient has.[4,5] Financial factors contributing to non-adherence include higher co-pay and co-insurances.[6] This necessitates the need to develop an intervention which is modifiable and can be tailored for individual patients.[1]

Due to the various causes of non-adherence, there is no one solution to addressing this issue. Additionally, some existing interventions that demand multiple visits to the pharmacy by either the patient or caregiver not only causes inconvenience to the patient but also interrupts the workflow of the pharmacist. Such interruptions can lead to declines in medication dispensing rates and gaps in the medication therapy further causing non-adherence.[7]

Addressing adherence with medication synchronization

An ideal adherence intervention should be one that addresses the multidimensional and dynamic nature of non-adherence. It should be able to improve access to care, be more convenient, educate the patients, and provide constant reminders. It should also help the patient monitor their own improvement and help them engage in mutual problem solving.[1]

One of the most recent proposed methods to address the above-mentioned issues in non-adherence is medication synchronization (med sync). Med sync is essentially refill synchronization. It is a process by which multiple chronic medications are refilled at the same time one day of the month instead of throughout the month.[1]

With med sync, the focus of the pharmacy staff changes from filling the prescription reactively upon the sudden request of the patient, to a more organized, synchronized and active pick-up or delivery of the prescription. This is a patient centric pharmacy care model, different from the traditional drug centric model.[8] This patient centric care model, emphasizes the preferences, values and needs of the patient. It means that the patient will participate actively in the shared decision making process.[9]

Study significance

Adherence plays a crucial role in the Centers for Medicare and Medicaid Services' (CMS) Star Rating system which is designed to assist Medicare beneficiaries in plan selection. Among the five measures used by CMS and Pharmacy Quality Alliance (PQA) for calculating the Star Rating, three of them are related to the medication adherence, therefore making adherence improvement a high priority.[7] With the development of the Medicare Star Rating System and the increase of commercial Part D plans, it becomes crucial to monitor the adherence subsequent health outcomes.[3] This implies that more empirical research is required to measure

adherence as a result of synchronization. Limited research has examined this phenomenon as only two studies have examined the impact of synchronization on adherence, using a matched cohort design and quasi-experimental study in which study patients were matched with control patients.[1,10] The current study had a pre-post research design, to strengthen the adherence literature related to medication synchronization.

Study objectives

The specific objectives of this study were to:

Assess the impact of medication synchronization on medication adherence for the following CMS Star Rating system drug classes:

1. Oral diabetes medications which include biguanides, sulfonylureas, thiazolidinediones, DPP-IV inhibitors, and meglitinides;
2. Hypertension medications which include renin-angiotensin system antagonists (RASAs) which includes angiotensin converting enzyme inhibitors (ACEs), angiotensin receptor blockers (ARBs); and
3. Cholesterol medications which includes statins.

CHAPTER II

LITERATURE REVIEW

Defining medication adherence

Before discussing how non-adherence might be addressed with med sync, it is important to first define medication adherence, and differentiate it from "compliance" and "persistence". *Medication compliance* is defined as "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen" and can be demonstrated when a patient's prescriptions are dispensed on a regular basis as prescribed by the physician. Whereas, *persistence* is defined as "the duration of time from initiation to discontinuation of therapy" and is a continuous variable represented by the total number of days for which the therapy was accessible. These terms sound similar but they are different because the clinical outcomes of the therapy depends upon both the medication as well as the duration for which the medications are consumed.[11] The difference between adherence and compliance is that compliance is considered to be passively following the instructions given by the physician whereas adherence occurs when both the patient and physician have mutually agreed upon the medication regimen.[12]

The problem of non-adherence

Looking at the case of chronic disease, non-adherence is a critical issue as almost 133 million people are suffering from at least one chronic disease in the US. Fifty percent of patients do not take their medicines properly, and 31% of them never get their original prescription filled.[13] Non-adherence can lead to problems such as medication ineffectiveness, increases in healthcare spending, hospitalizations, and emergency room (ER) visits.[12] It has been reported that non-adherence causes almost 125,000 deaths in the US and incurs a cost of $177 billion

annually.[14] Chronic diseases such as hypertension, diabetes, hypercholesterolemia and congestive heart failure (CHF) are among the most prevalent, costly, or both; therefore addressing medication adherence related to these disease states becomes critical.[13]

With regard to persistence, adherence achieved in chronic disease states have been reported to worsen, dropping after the initial 6 months of the therapy itself. In clinical trials, adherence tends to be more ideal than world scenarios, even then, adherence achieved in chronic illness patients is low, ranging from 43 to 78%. The consequences of non-adherence are significant, including exacerbation of the disease, higher mortality, increased healthcare costs, and increased hospitalizations. Thirty-three percent to 69% of hospitalizations in the US are attributed to non-adherence and incur $100 billion annually.[12]

The causes of non-adherence

The six patterns of medication taking behavior found among patients with chronic illnesses helps to explain the prevalence of non-adherence. One-sixth of patients attain near perfect adherence; one-sixth consume almost all the doses but at irregular times, one-sixth occasionally skip single day doses and take doses at irregular times, one-sixth take drug holidays about 3-4 times in annually while skipping doses occasionally, one-sixth take drug holidays every month with and skip medications frequently, and one-sixth consume few or no doses while trying to appear as though they are adherent.[12]

The causes of non-adherence are many and varied. The World Health Organization (WHO) has classified five factors as major underlying causes for non-adherence. The first factor includes individual characteristics such as physical condition, cognitive abilities, and demographics such as age, gender and race. The second factor includes a patient's medical condition including asymptomatic condition and comorbidities. The third factor includes the

health system in which the patient lives and the type of care the patient receives. The fourth factor includes the complexity of therapeutic regimen and fifth factor includes all the socioeconomic barriers patient faces. Osterberg goes on to note that non-adherence factors include complicated therapeutic regimens, improper explanation of benefits and side effects of the medication, lack of concordance with patient lifestyles, and poor patient-physician relationships.[12]

Outcomes and costs of non-adherence in chronic disease

As previously discussed, chronic diseases are victim to the issue non-adherence the most. Considering the example of diabetes mellitus, non-adherence is one of the most prevalent issues leading to unfavorable outcomes. In a study, the unadjusted analysis states that diabetic non-adherent patients have higher percentage of having all cause hospitalization (23.2% vs 19.2%, $p < .001$) and all-cause mortality (5.9% vs 4.0%, $p < .001$) as compared to adherent patients. It has also been observed that less than half of the patients consuming statin medications remained adherent to the therapy after 12 months of starting the therapy. Results of a multivariable analysis of this study was in agreement with the results above. Increased risk for all cause hospitalization (OR, 1.58; 95% CI, 1.38-1.81; $p < .001$) and all-cause-mortality (OR, 1.81; 95% CI, 1.46-2.23; $p < .001$) was observed. Cumulative results were consistent with the results of the individual categories such as oral hypoglycemic, antihypertensive and statin medications. It was found that with a 25% rise in adherence of antihypertensive medications, an associated decrease of -1.0mm Hg and -1.2 mm Hg in systolic and diastolic blood pressure was observed. Similarly, with a 25% increase adherence to oral hypoglycemic and statins a reduction of -0.05% and -3.8mg/dL was observed in HbA1c and LDL-C levels respectively. In this study combined reduction in the magnitude of hospitalization and mortality was higher than what was anticipated

given the changes in the intermediate measure. This indicates that adherence might also be related to self-care behaviors that may or may not be directly related to the final outcomes. Looking at the importance and consequences of non-adherence, we can conclude that medication adherence should be assessed by the healthcare providers on a regular basis.[15]

The systematic literature also indicates that due to non-adherence to oral hypoglycemic medications, only 43% of the diabetic patients have glycosylated hemoglobin levels under 7% as recommended by American Diabetes Association. For hypoglycemic agents, a range of 13% to 64% was found for total number of non-adherent patients.[16] Lower levels of Medication Possession Ratio (MPR), a measure of medication adherence was also found to be correlated with higher costs. MPR can be defined as "Ratio of the number of days' supply dispensed to a patient, divided by the number of days in the cohort period, typically a year". MPR of 60% is found to be associated with mean total cost of $8,699. Whereas, a 10% increase in the MPR can be correlated to reduction of 8.6% in total annual healthcare costs. It has been noted that HbA1c levels lesser than 8% and HbA1c greater than 10 incurred a cost of $4,475 and $8,088, respectively.[14,16] Financially, incident cases are more expensive than prevalent cases and gestational diabetes cases are more expensive than type-2 diabetes cases.[16] These findings strongly emphasizes on the importance of medication adherence with respect to both healthcare cost and healthcare utilization.

Bolstering the above findings, another study focusing on the causal link between medication adherence and health care use and cost for four vascular diseases (hypertension, diabetes, dyslipidemia, and congestive heart failure (CHF)) was conducted. Results indicated that although increase in medication adherence causes an in increase total pharmacy costs, it helps in saving a substantial amount of money by reducing overall expenditure in hospitalizations

particularly linked with inpatient hospital days and ER visits. Hospitalizations and ER visits are of priority as they are the key drivers of healthcare costs. Results indicate that adherence in dyslipidemia and CHF can be associated with fewer inpatient hospital days, ranging from 1.18 fewer days to 5.72 fewer days respectively. The average benefit-cost ratio due to medication adherence for CHF, hypertension, diabetes and dyslipidemia can be given as 8.4:1, 10.1:1, 6.7:1 and 3.1:1 respectively. Financial gains resulting from better adherence truly justifies adopting adherence management programs that can lead to considerable medical savings. Results also recommend the use of pharmacist-led patient counseling as a promising intervention to improve adherence at lower expenses.[13]

Another study evaluating the impact of adherence on healthcare utilization and cost for diabetes, hypertension, hypercholesterolemia and CHF was performed. For diabetes and hypercholesterolemia, low disease-related medical costs were found to be correlated with higher levels of medication adherence and these higher levels were associated with significantly fewer hospitalizations. For hypertension, hypercholesterolemia and diabetes, pharmacy cost was offset for all-cause medical cost at relatively higher levels of medication adherence. It can be inferred that benefits gained due to increased prescription drugs (due to improved adherence) is worth the added cost.[17]

Another study was conducted focusing on finding the association between medication adherence and utilization for acute healthcare services. Results of logistic regression analyses suggested that adherence was a significant predictor of all-cause hospitalizations and ER visits. It was observed that chances of all-cause hospitalization and ER visits among the adherent patients were 40% less in patients with diabetes, 44% less in patients with hypercholesterolemia and 35%

less in patients with hypertension. These findings imply that policy makers should focus on interventions that can improve adherence leading to other benefits.[18]

Addressing non-adherence

Considering the importance of adherence in a multidimensional aspect, it becomes crucial to employ interventions that can improve adherence which can lead to reduction in total healthcare cost. One of the most crucial reasons to focus on adherence comes from the Centers of Medicare and Medicaid Services (CMS). CMS evaluates Medicare Part D plans on the basis of Star Rating system ranging from one to five stars. Star Rating consist of four sections, one of which is categorized as pricing and patient safety. This section consists of measures evaluating medication adherence for oral diabetes agents, hypertension agents and cholesterol agents. Star Rating are useful in making quality based payments to Medicare Advantage Plans (MA-PDs) and selling benefits to prescription drug plans (PDPs).[19]

As stated in a Chain Drug Review article, MA-PDs cannot achieve the five-Star Rating without active and effective participation from community pharmacies that create quality patient outcomes.[19] In agreement, the 2012 WHO report stated that interventions aiming at improving medication adherence are more capable of improving health of people than any other medical intervention.[19] It has been reported that that five out of every six pharmacist directed adherence interventions can improve the adherence of patients ranging from 7% to 27%. Pharmacist-led interventions have approximately 83% successfully adherent patients as compared to 67% adherent patients in electronic interventions with no involvement of humans, 38% adherent patients in phone calls lead interventions and 38% adherent patients involved in clinic programs making the role of pharmacists important in the adherence management program.[1] Interventions that can help to reduce wait times and improve the communication between physicians and

patients could be more beneficial. Patients who often miss their appointments are those who may require assistance the most to become adherent. They can be helped by providing increased information, motivation and imparting behavioral skills.[12,20]

Considering the dynamic and multidimensional nature of medication adherence, especially in chronic diseases as stated above, medication synchronization (med sync) may be a solution to managing medication adherence. Med sync is a process of coordinating multiple chronic medications of a patient to be picked-up or delivered on one day each month.[1] There are several med sync programs available on the market such Elite Care, MedSync, SyncYourMeds, HealthyPackRx, RxSync, SimplifyMyMeds, TimeMyMeds and the Appointment Based Model (ABM).

Medication synchronization – how it works

One of the major steps of the med sync process is to identify ideal patients for the program. Patients using multiple chronic medications and making multiple visits to the pharmacy in a month are the best fit for the program. Multiple monthly visits made by the patient to the pharmacy should be taken into consideration. Patients who visit the pharmacy multiple times per month to maintain their social network may not be good candidate for med sync.[21]

Once a patient is deemed a good candidate for med sync, the anchor drug must be identified. An anchor drug is defined as the drug around which the first synchronization date is identified.[1,21] The cost of the drug, amount of co-pay and out-of-pocket costs are among the various deciding factors for the anchor drug selection.[7]

Selection of the chronic drugs to be synchronized is another important component in the initiation of the program. Not all the chronic drugs are eligible for the inclusion in the program. Chronic drugs such as sedative hypnotics, anxiolytics and analgesics are not recommended for

the enrollment in the synchronization process. Other chronic medications inappropriate for the synchronization includes those with non-standardized doses such as insulin, creams, eye drops and inhalers and drugs with varying cycles such as bisphosphonates, oral contraceptives and vitamin D. Pre-written Schedule II prescriptions and medications in unbreakable packaging are not good candidates for synchronization. Drugs treating hypertension, diabetes, and hypercholesterolemia are among the suitable candidates.[7]

While selecting first synchronization date, the pharmacist should provide patients with short fills and long fills depending upon the doses remaining on the patient's current prescriptions. Short fills are for a less than usual supply whereas long fills are dispensing medication more than the typical supply.[8] This avoids disruption in the continuity of therapy.[1] Alternatively, the pharmacist or technician may contact the physician to reauthorize all new refills for a patient for 28 or 30 days. Once the drugs to be synchronized are decided, they are documented in a pre-appointment call sheet.

A week before the appointment day the pharmacist or technician calls the patient to check about changes in the medication regimen, if any. This call differentiates med sync from other automatic refill programs as it is an opportunity to gain meaningful information about the patient which is not possible during an automated call.[8] Additionally, it develops a sense of being cared for in the patient's mind and the perception that a complete health system is attempting to help them to have a healthier life.[8] Additionally, the pharmacist or technician identifies any problems with medication adherence and any medical issues of concern. Once the call is complete, the pharmacist or technician adjudicates and processes the prescriptions in preparation for filling the prescriptions. Any insurance related issues are also resolved at this time.

Three days before the appointment day, the pharmacist or technician fills the prescription for subsequent pick-up or delivery. The day before the prescription is due or even that day, depending upon the preference of the patient, the medication is either collected by them or is delivered to them by the courier (or mail service if delivered earlier).[22] In some med sync programs, patients who fail to pick-up their medication on the pick-up day are contacted by the pharmacist.[21]

Physicians play a critical role throughout the process. It is the responsibility of the pharmacist to inform the physician if their patients enroll in med sync. A formal letter should be mailed to the physician with a request to refill the synchronized medications.[1,7] Communication with the physician helps the physician gain additional information about the patient who is enrolled in med sync.

Benefits of medication synchronization

Benefits to patients. Med sync is argued to be beneficial in improving the overall adherence of a patient in several ways. Fewer number of pharmacy visits may lead to better medication adherence and promote continuity of care, thereby improving access to care.[1] Unlike traditional, reactive, prescription filling, med sync prescriptions get filled within a week of the pick-up or delivery date leading to reduction in medication gaps and unavailability of medicines. By the time patient reaches the pharmacy to pick-up their medication their insurance has already been processed resulting in more convenience.[1] In some med sync programs, the monthly appointment with the pharmacist gives the pharmacist an opportunity to clarify, modify, and enhance the patient's medication therapy leading to a reduction in possible medication errors.[1] Monthly phone calls (and appointments, if used) helps the pharmacist educate the patient and involve them in solving drug-related and adherence problems related to lack of affordability,

physical impairment, low health literacy and shortage of social support. Synchronization simplifies the medication regimen and provides constant progress updates and feedback to the patient and the patient's physician.[1,3]

Med sync helps manage medications with greater therapeutic complexity, leading to improved outcomes.[1] Synchronization takes care of the preference of the patient with regard to the payment, delivery and mode of contact as well. Patients have the choice to either pick up their medication or receive it by mail or courier. They can pay for the medication by either a single monthly payment or have the option to split it up in several monthly installments. Patients can be contacted by cell phone, home phone or even email.[1]

Benefits to pharmacists. Med sync allows the pharmacist to step out from behind the counter and provide patients with the healthcare and clinical services they require. Better management of pharmacy work flow is an advantage as everything taking place at the pharmacy is pre-planned and proactive. The frequency of phone calls is reduced as the system is more structured, yielding substantial time savings and more organized staff.[3] It improves the overall business in the pharmacy by increasing the prescription revenue and gives an opportunity to provide Medication Therapy Management (MTM) services and additional clinical services like immunizations and flu shots.[1] Med sync also reduces the total number of random visits made by the patients, which helps in managing the disorder in the pharmacy and also helps to reduce the stress levels of the pharmacist working there.[8] To summarize, med sync promotes the achievement of overall operational efficiency of the pharmacy.[21]

Med sync allows the pharmacist to better perform in their role as a healthcare provider. They can offer suggestions regarding over-the-counter medications and guide the patient towards a better diet, lifestyle changes and needed home equipment.[3] It also allows the pharmacist to

provide Medication Therapy Management (MTM) services to the patient, and possibly be reimbursed for these services. As an added advantage, the outcome data collected in this process are often used to incentivize pharmacists which motivates pharmacists to perform better.[8]

In terms of business, med sync can give fruitful returns for the invested labor. Findings state that prescription revenue has gone up by 29% for patients who are associated with the pharmacy for a year or more by using Elite Care which is a med sync program offered by Red Cross pharmacy.[3]

Benefits to physicians. Physician-pharmacist communication that occurs when enrolling patients for med sync serves as opportunity to educate the physician about the advantages of med sync and gather support from them.[7] The literature suggests that physicians are pleased with med sync programs and improvement in medication adherence, and receiving feedback related to adherence.[21] As stated by a pharmacist based in Colorado, with the help of med sync programs, pharmacists have taken the time consuming part of the physician's job, and that physicians truly appreciate it.[8]

Challenges of medication synchronization

The challenges associated with med sync include identifying and enrolling patients, identifying anchor dates and drugs, differentiating sync patients from the non-sync patients, managing short-fills and long fills.[2] While dispensing short fills and long fills to reach a sync date, the pharmacist needs to address insurance issues as well. Because all of a patient's prescriptions are being dispensed on the same date, the pharmacist needs to manage and calculate the co-pays carefully. This can be more difficult when dealing with Medicare Part D patients who are moving into the donut hole[21] and Medicaid patients who may have a prescription cap. Pharmacists should make patients aware of the possible one-time cost

associated with the co-pays and out-of-pocket costs related to the short fills received just before the first sync date.[7]

Considering that the role of pharmacist is crucial in the successful implementation and maintenance of med sync, pharmacists and their staff need to be constantly educated on a regular basis. Educational materials may include modules related to patient centered care, prescription synchronization techniques, maintenance of proper documentation, methods to foster mutual problem solving, and providing MTM services. Having improved and efficient technology might also results in easier implementation and scalability of med sync helping in creating and storing data which can be of help to prove the program's worthiness in the future.

Med sync research findings

In a study conducted by a joint collaboration of the National Community Pharmacists Association (NCPA) and Ateb Inc., investigators measured the impact of Ateb's Time My Meds synchronization program on medication adherence. They created a study group and matched it with a control group. Results indicated that Time My Meds made a substantial improvement in the medication adherence of the patients and also helped in increasing the pharmacy's revenue and total gross margin.[10]

Another study was conducted by Virginia Commonwealth University (VCU) with Thrifty White Pharmacy, a chain of employee-owned community pharmacies. In this study, the Appointment Based Medication (ABM) med sync model was used. Investigators utilized a quasi-experimental research design while matching the study patients to the control. It resulted an increase in the adherence of the patients and also showed a decreased probability of non-persistence. Specifically, it was reported that by increasing a diabetic patient's medication adherence from 40-59% $4,091 can be saved per patient.[3] With 25.8 million diabetic patients in

the US, the amount of savings could be phenomenal. This study also reflected an increased level of adherence among study patients as compared to the control patients. Patients enrolled in the med sync had adherence rates of 66.1%-75.5% as compared to the control patients with 37%-40.8% for initial one year. In terms of odds of adherence, study patients had 3.4-6.1 times higher odds of adherence compared to control.[1] A follow-up study conducted for Thrifty White's study displayed increased adherence with med sync program. It resulted in a significant drop in the cost of healthcare with patients having hypertension, diabetes and increased cholesterol levels.[22]

Due to med sync's positive results and improvement in adherence, almost 250-350 people a week enroll in med sync at Thrifty White Pharmacy. Most of the patients enrolled in the study were 40 to 55 years old. People in this age group are those who are working and have a busy schedule. Providing reminders for their medication can be helpful for them to maintain their health in their hectic life style. Overall, med sync has been successful in yielding positive results by improving medication adherence of patients. This is well reflected in both patient satisfaction surveys as well as the talks done with the payers.[22]

Summary

These findings combined with the importance of medication adherence for the healthcare system makes further empirical examination of med sync an important step toward better medication use outcomes and lowered healthcare spending. In fact, state legislatures are recognizing this importance. For example, Missouri was one of the first states to propose a bill stating that pharmacies providing medication synchronization should be reimbursed for the short fills dispensed for the reason of synchronization.[23] Continued research using alternative study designs are necessary for understanding the role of med sync in medication adherence management.

CHAPTER III

METHODS

Study design

A quasi-experimental pre-post study design was employed for this study using pharmacy prescription fill data from various independent community pharmacies located in different regions of Mississippi. Patients were compared on the main outcome measure, medication adherence, before and after the medication synchronization intervention. Because this study employed a pre-post study design, patients served as their own control.

A six month pre and post study period was used to measure adherence. Analyses were conducted separately for each of the drug classes under the CMS Five-Star Quality Rating System. Drug classes in the CMS Five-Star Quality Rating System include *oral diabetes medications, hypertension medications and cholesterol medications*.

The total study period for each patient was one year, including the pre- and post-study period. Patients' medication adherence was calculated for a six month period before the index date and a six month period after the index date. The index date was used to separate the pre- and post period of each patient. *Index date* was defined as the first med sync date when the patient received his first fill of the prescription after enrollment in the med sync program. Index date (also termed med sync date) was agreed upon by the pharmacist and the patient, and on this date all prescriptions were dispensed at the same date every month. Each patient was flagged on their specific index date in the data indicating the start of the med sync program. This flag was used to separate the pre and post intervention period. The post period of six months was a part of the treatment period. *Treatment period* was defined as time beginning from the index start date

(ISPD) until the last day of post period or end of measurement period or until death or until discontinuation from the med sync program. This study received an approval from the Institutional Review Board (IRB) of The University of Mississippi.

Data extraction

Pharmacy prescription fill data was collected for the dates January 1, 2008 until the date investigators visited the pharmacy (hereafter called as the measurement period). Med sync patients were identified until the time each patient had sufficient post period of six months so as to have a sufficient time frame to measure post period (post-index date) medication adherence for enrolled patients. Each patient had their own index date and based upon that a unique and separate pre-post period.

Sample description

A convenience sample of independent community pharmacies practicing medication synchronization was used for identifying med sync patients. Selected pharmacies were situated in various regions of Mississippi therefore reducing the geographical bias. All med sync patients having a prescription fill history in the measurement period within each pharmacy and satisfying the inclusion and not eliminated by exclusion criteria (described below) were used for analysis.

Table 1 outlines a convenience sample of independent community pharmacies used for the study. Before extracting data from the pharmacies, a Data Use Agreement (DUA) was also executed between each pharmacy and the University of Mississippi. All patients having a prescription fill history in the measurement period within each pharmacy were taken. While performing the analysis patients meeting the inclusion criteria and not eliminated by exclusion criteria (described below) were used.

Table 1: Convenience Sample of Pharmacies

Store name	*Pharmacist contact*	*City*
Gene Polk's Pharmacy	E. Brinson Polk, Jr.	Magee
Iuka Discount Drugs	Chris Cornelison	Iuka
Thrift Drugs	Marty Bigner	McComb
Tyson Drug Co	Bob Lomenick	Holly Springs

Inclusion criteria

Patients were enrolled in med sync program offered by their pharmacy. Patients at least 18 years of age were included in the study. Every patient taking prescription medications belonging to the following drug classes were included in the analysis: *Oral diabetes medications* which included biguanides, sulfonylureas, thiazolidinediones, DPP-IV inhibitors and meglitinides; *hypertension medications* which included renin-angiotensin system antagonists (RASAs), angiotensin converting enzyme inhibitors (ACEs), angiotensin receptor blockers (ARBs); and *cholesterol medications* which included statins. Patients taking these medications in oral dosage form, only, were included in the analysis. Patients had to have an index date in order to meet the requirements of a pre-post design. Patients having a continuous prescription history of at least 180 days (six months) before and after the index date were included in the analysis.

Exclusion criteria

With regard to prescription transactions, records for insulins and incretin mimetics (administered by subcutaneous injection), were removed before analysis due to inability to synchronize refills of these medications. Patients having a continuous gap equal to or more than 90 days during the observation period were also excluded assuming that they have discontinued taking the medications. Also, patients having missing values for age or date of birth were

removed from the analysis. This was done in order to comply with the IRB regulations of including patients only with greater than or equal to 18 years of age.

Sample size

Wilcoxon Signed-Rank Tests was performed in order to assess any changes in medication adherence from the pre-period to the post-period. Sample size requirements for Wilcoxon Signed-Rank Tests were calculated using G*Power. According to result obtained by G*Power, a total sample size of 82 patients (number of pairs) was needed in order to perform a Wilcoxon Signed-Rank Tests with a medium effect size of 0.3 and alpha level of 0.05 to obtain a power of 80% assuming we use minARE as the parent distribution. When the parent distribution is unknown, then "minARE" is used as the parent distribution while performing the sample size calculations. Also, the value of effect size (0.3) was chosen for this test. It is the standard value used to obtain a medium effect size which can be used for sample size calculations for the Wilcoxon Signed-Rank Test for matched pairs.[24] Considering the analysis was be performed separately for the three drug classes, we required 82 patients' pairs in each of the drug classes for the analysis. A brief synopsis of the above sample size calculations for Wilcoxon Signed-Rank Test for paired data is provided in Table 2 below:

Table 2: Sample Size Calculation for Wilcoxon Signed-Rank Test for Paired Data

	Alpha	*Power*	*Medium Effect Size*	*Distribution*	*Total Sample Size (N= # of pairs)*
Diabetes	0.05	0.8	0.3	minARE	82
Hypertension	0.05	0.8	0.3	minARE	82
Cholesterol	0.05	0.8	0.3	minARE	82

When assessing the study outcome, patients having a PDC greater than or equal to 80% were considered "adherent" and patients having a PDC less than 80% were considered "non-adherent". A dichotomous flag variable was created by flagging adherent patients as "1" and non-adherent as "0". The proportion of individuals who were adherent was calculated for the pre- and post- periods using this dichotomous flag variable. In order to assess the significance of the difference between two correlated proportions, McNemar's Test was performed. G*Power was used for sample size calculations for this analysis test, and sample size calculations were calculated separately for the three CMS Star Rating system drug classes. In order to calculate sample size, the value of the proportion of discordant pairs and odds ratio of being adherent in post period as compared to pre period in the G*Power was needed. *Discordant pairs* are those patients who are adherent in pre-period and non-adherent in post-period ("Adherent"~"Non-Adherent") OR those patients who are non-adherent in pre-period and adherent in post-period ("Non-Adherent" ~"Adherent"). Whereas, *concordant pairs* are those patients who are adherent

in pre as well as post period ("Adherent" ~"Adherent") OR those patients who are non-adherent in pre- as well as post-period ("Non-Adherent" ~"Non-Adherent"). The proportion of discordant pairs can be calculated by the sum of the proportion of discordant pairs in pre-period (P_{pre}) and the proportion of the discordant pairs in post-period (P_{post}) i.e. PD= (P_{post} +P_{pre}). Considering data was not collected at the time of sample size calculations, the values of the proportion of discordant pairs in pre-period (P_{pre}) and post-period (P_{post}) were unknown, the following approximation formula was used to calculate proportion of discordant pairs (PD): Pt (1-Ps) + Ps (1-Pt). Where, Pt is the proportion of adherent patients in post-period and Ps is the proportion of adherent patients in pre-period. This provided an estimate of the PD for the sample size calculation. The odds ratio was calculated by dividing the proportion of discordant pairs in post-period by the proportion of discordant pairs in pre-period, i.e., P_{post}/P_{pre}. It is proved that, Pt=Ps is equivalent to $P_{post}=P_{pre}$, therefore the odds ratio was calculated by Pt/Ps.[25]

- *Oral medications including biguanides, sulfonylureas, thiazolidinediones, DPP-IV inhibitors, and meglitinides*. According to the performance scores calculated on Mississippi Medicare data for the year 2007, approximately 18.20%, 33.3% and 41.5% patients (18 years and older) were found to be adherent (meeting PDC threshold of 80%) to oral diabetes medications (Thiazolidinediones, Biguanides and Sulfonylureas respectively). According to guidelines given by the CMS Star Rating system (Prescription Drug (Part D) Plans, i.e., PDP) a pharmacy needs to have a percentage of adherent patients between $\geq$ 79% and < 82% in order to achieve 3 stars in the CMS Star Rating system. For the purpose of this analysis the proportion of adherent patients in the pre-period was assumed to 0.182, 0.333 and 0.415 (Ps) for Thiazolidinediones, Biguanides and Sulfonylureas respectively and proportion of adherent patients in the post period is assumed to be 0.8199 (Pt). The

proportion of discordant pairs (PD) was 0.7034564, 0.6068466 and 0.554383 and odds ratio was 4.504945055, 2.462162162 and 1.975662651 for Thiazolidinediones, Biguanides and Sulfonylureas respectively (calculated using the formulas listed above). Using these values and alpha level of 0.05 and a power of 0.80; 19, 58 and 109 pairs were required to perform the original McNemar's Test. Taking these sample sizes into consideration, a conservative estimate of 109 pairs was required for the purpose of analysis of oral diabetes medications drug class.

- *Hypertension medications including ACEs/ARBs*: According to the performance scores calculated on the Mississippi Medicare data for the year 2007, approximately 40.00% patients (18 years and older) were found to be adherent (meeting PDC threshold of 80%) to hypertension medications (ACEI/ARBs). According to guidelines given by the CMS Star Rating system under the PDP, a pharmacy needs to have percentage of adherent patients between ≥ 76% and < 81% in order to achieve 3 stars in the CMS Star Rating system. For the purpose of this analysis the proportion of adherent patients in the pre-period was assumed to be 0.40 (Ps) and proportion of adherent patients in the post period was assumed to be 0.8099 (Pt). The proportion of discordant pairs (PD), i.e., 0.56198 and odds ratio, i.e., 2.02475 was calculated using the formulas listed above. Using these values and alpha level of 0.05 and a power of 0.80; 95 pairs were required to perform the original McNemar's Test.
- *Cholesterol medications including statins*: According to the performance scores calculated on the Mississippi Medicare data for the year 2007, approximately 28.90% patients (18 years and older) were found to be adherent (meeting PDC threshold of 80%) to cholesterol medications (statins). According to guidelines given by CMS Star Rating system under the PDP, a pharmacy needs to have percentage of adherent patients between ≥ 69% and < 75%

- in order to achieve 3 stars in the CMS Star Rating system. For the purpose of this analysis the proportion of adherent patients in the pre-period was assumed to be 0.289 (Ps) and the proportion of adherent patients was assumed to be 0.7499 (Pt). The proportion of discordant pairs (PD), i.e., 0.6 and odds ratio, i.e., 2.6was calculated using the formulas listed above. Using these values and alpha level of 0.05 and a power of 0.80; 50 pairs were required to perform the original McNemar's Test. Calculations for the original McNemar's Test are provided in Table 3 below:

Table 3: Sample Size Calculation for McNemar's Test

	Post Period (Pt)	*Pre Period (Ps)*	*Proportion of Discordant Pairs (PD)*	*Odds Ratio*	*Alpha*	*Power*	*Total Sample Size (N= # of pairs)*
Diabetes	0.8199	0.415	0.554383	1.98	0.05	0.80	**109**
Hypertension	0.8099	0.40	0.56198	2.02	0.05	0.80	**95**
Cholesterol	0.7499	0.289	0.6054578	2.60	0.05	0.80	**50**

Data collection

Study investigators visited the pharmacies to collect data for this study. A DUA was executed between each pharmacy and the University of Mississippi before data collection. All the prescription fill data was transferred from the computer system to a flash memory drive. As soon as the data was collected, the patient identifiers were converted into a de-identified format

by encrypting the patient identifiers assigned by the pharmacy. All Data File(s) were installed on a secure, stand-alone, non-networked access computer maintained in the School of Pharmacy, housed in a secure Center for Pharmaceutical Marketing and Management (CPMM) Data Center. The study was approved by the Institutional Review Board (IRB) of The University of Mississippi.

Data management

All the pharmacy data was pulled, cleaned, processed and analyzed with the help of Statistical Analysis Software 9.4 (SAS®, SAS Institute, Cary, NC). Based on the National Drug Code (NDC) of the drugs; prescription records were assigned to their respective therapeutic classes as classified by CMS Star Rating system. Detailed list of all the drugs with their NDCs, which are included in the PQA Measure of Proportion of Days Covered (PDC) for oral diabetes medications, hypertension medications and cholesterol medications was used for the purpose of this study. All the original collected data was stored on the secured server in order to maintain the security and privacy of the data and participating individuals. Patient identifiers were converted into an encrypted format by de-identifying the patient identifiers. Later in the analysis, patients were identified in the pharmacy database with their help of their de-identified patient identifiers. Patients were identified as a part of the med sync program with the help of their index date specified by the pharmacist.

Measures

Proportion of days covered (PDC) was used to calculate the adherence of patients in the study. PDC is the preferred measure of adherence by the PQA. The mathematical formula PDC is given as below:

$$\text{PDC} = \frac{\text{Number of days the patient is covered by the drug in the study period}}{\text{Number of days in the study period}}$$

PDC helps to achieve a conservative estimate of the medication adherence especially when a patient consumes *more than one* medication for their treatment. Considering the current study focusing on med sync, whereby the patients of interested consumer more than one chronic prescription drug per month; the use of PDC as an adherence measurement became more relevant. PDC is always helpful in adjusting for the gaps in therapy and also adjusting for overlap in therapy. While doing the calculations for PDC, a day is only counted if the patient has medication in his or her possession. PDC values can range from zero to one. The assumption that we make while using such a measure, is that, when a medication is possessed the medication is assumed to be consumed as well.[26] Patients having PDC equal to or greater than 0.80 were considered adherent. According to the measure, if multiple prescriptions for the same generic drug are given on the same day or different days with overlapping days' supply, adjustment should be made to the prescription start date, so that the start date for the same second generic drug is the day after the previous fill has ended. Same adjustment was performed while calculating the PDCs for the study participants.

Data analyses

Data analysis was conducted using SAS software (version 9.4; SAS Institute, Cary, NC). Descriptive statistics of the sample after applying inclusion-exclusion criteria were calculated for each of the therapeutic drug classes separately. Descriptive statistics included calculating means, frequencies and percentages as appropriate.

For assessing study objectives, PDC scores for the pre and post periods for each patient in the study were calculated. Patients having a PDC value of 0.80 or more were considered "adherent" and PDC less than 0.80 were considered "non-adherent". A dichotomous flag

variable was created, in which adherent patients will be flagged as "1" and non-adherent patients were flagged as "0". Because this study uses a pre-post design, patients served as their own control. Patients' PDC values before and after the index date were calculated. Mean and median PDC scores of pre and post periods for each of the three CMS drug classes were obtained. Considering the paired nature of the observations and non-normality of the PDC scores (proportion), Wilcoxon Signed-Rank Test for paired data was used to compare the PDC scores of pre and post periods for each of the three drug classes separately. An alpha level of 0.05 was used for the Wilcoxon Signed-Rank Test for the paired data, obtaining a p-value lesser than 0.05 lead to the rejection of the null hypothesis helping us to infer that the pre-period and post-period scores are statistically different from each other. Secondly, the proportion of adherent patients in the pre-period was compared to the proportion of adherent patients in the post-period for each of the three therapeutic drug classes separately. In order to calculate this proportion, the numerator included all those patients meeting the inclusion/exclusion criteria and flagged as "1". Whereas, the denominator included all those patients meeting the inclusion/exclusion criterions and flagged as "1" or "0" both. An alpha level of 0.05 was used for this test, obtaining a p-value lesser than 0.05 lead to the rejection of the null hypothesis and helped us to infer that the marginal proportions are significantly different from each other. After performing the McNemar's Exact Test a 2x2 contingency table was obtained to calculate the odds of adherence in the post-period as compared to the pre-period. McNemar's Exact Test was performed for each of the three drug classes separately.

CHAPTER IV

RESULTS

Sample description

Prescription transaction data was collected from Thrift Drugs, Gene Polk's Pharmacy, Tyson Drugs Co and Iuka Discount drugs. An initial list of total 126, 139 and 146 synchronized patients containing index date and enrollment date information was obtained from Gene Polk's Pharmacy, Tyson Drugs Co and Iuka Discount drugs pharmacy respectively. Due to the unavailability of index date and enrollment date information at Thrift Drugs Pharmacy, all of their prescription transaction data was discarded and Thrift Drugs pharmacy was excluded from the study. Data from the remaining three pharmacies was combined and patients were assigned to their respective drug classes by matching the NDC numbers present in their prescription transaction records with the list of the NDCs provided by PQA for each of their drug classes.

Multiple patients contributed to more than one drug class considering that many of them were taking multiple drugs belonging to more than one drug category. Separate datasets were created for diabetes, hypertension and cholesterol categories. Inclusion and exclusion criteria were applied to each of the drug categories separately for the purpose of analysis.

A total of 56, 89 and 77 patients were found to meet the inclusion/exclusion criteria in diabetes, hypertension and cholesterol drug categories, respectively. The average age of the patients was approximately 66 years (23-87 years, ± 11.03), 70 years (41-101 years, ± 11.53) and 67 years (40-100 years, ± 11.85) in diabetes, hypertension and cholesterol drug categories, respectively. The sample predominantly belonged to those patients who were falling in the age category of 60-80 years (Table 4).

Table 4: Distribution of Patients by Age

Age Categories	*Diabetes (%)*	*Hypertension (%)*	*Cholesterol (%)*
18-40	1 (1.79)	0	0
40-60	8 (14.29)	13 (14.61)	19 (24.68)
60-80	**43 (76.79)**	**59 (66.29)**	**48 (62.34)**
80-100	4 (7.14)	15 (16.85)	9 (11.69)
100+	0	2 (2.25)	1 (1.30)
Total	56 (100)	89 (100)	77 (100)

Patient PDC values

Using the prescription transaction data, proportion of days covered (PDC) was calculated for the pre-period and post-period. Each patient had a unique index date, and depending upon that index date, their own pre-period and post-period. The results indicate that 47 (83.93%), 67 (75.28%) and 59 (76.62%) patients belonging to the diabetes, hypertension and cholesterol drug categories, respectively, had PDC values in the range of 90-100 in the pre-period. Whereas in the post-period, almost 54 (96.43%), 87 (97.75%) and 74 (96.1%) patients belonging to diabetes, hypertension and cholesterol drug categories, respectively, had PDC values in the range of 90-100. Results indicate an appreciable increase in the number of patients whose PDC values were in the range of 90-100. A full description of the distribution of patients falling in various PDC categories are presented in Table 5.

Table 5: Distribution of Patients Belonging to PDC Categories in Pre- and Post-Period

	Proportion of Days Covered (PDC) Categories						
	30-40 (%)	*40-50 (%)*	*50-60 (%)*	*60-70 (%)*	*70-80 (%)*	*80-90 (%)*	*90-100 (%)*
Diabetes							
Pre-Period	1 (1.79)	1 (1.79)	1 (1.79)	1 (1.79)	1 (1.79)	4 (7.14)	**47 (83.93)**
Post-Period	0	0	0	0	0	2 (3.57)	**54 (96.43)**
Hypertension							
Pre-Period	0	0	4 (4.49)	3 (3.37)	2 (2.25)	13 (14.61)	**67 (75.28)**
Post-Period	0	0	0	0	1 (1.12)	1 (1.12)	**87 (97.75)**
Cholesterol							
Pre-Period	0	0	3 (3.9)	2 (2.6)	2 (2.6)	11 (14.29)	**59 (76.62)**
Post-Period	0	0	0	0	1 (1.3)	2 (2.6)	**74 (96.10)**

Patients PDC values categorized by age

A cross-table was also created between age categories and PDC categories in the pre-period as well as the post-period. This information is provided in Table 6 below for diabetes, hypertension and cholesterol drug categories, respectively. A majority of the patients were between 60 and 80 years and had PDC values ranging from 90 to 100 during both the periods in all the three drug categories.

Table 6: Patient PDC Values Categorized by Age

	Age Categories				
	18-40 (%)	*40-60 (%)*	*60-80 (%)*	*80-100 (%)*	*100+ (%)*
Diabetes					
Pre-Period					
30-40	0	0	1 (1.79)	0	0
40-50	0	0	1 (1.79)	0	0
50-60	0	0	1 (1.79)	0	0
60-70	0	0	1 (1.79)	0	0
70-80	0	0	1 (1.79)	0	0
80-90	0	1 (1.79)	3 (5.36)	0	0
90-100	1 (1.79)	7 (12.50)	**35 (62.50)**	4 (7.14)	0
Post-Period					
80-90	0	1 (1.79)	1 (1.79)	0	0
90-100	1 (1.79)	7 (12.50)	**42 (75)**	4 (7.14)	0
Hypertension					
Pre-Period					
50-60	0	0	2 (2.25)	2 (2.25)	0
60-70	0	1 (1.12)	1 (1.12)	1 (1.12)	0
70-80	0	0	2 (2.25)	0	0
80-90	0	0	13 (14.61)	0	0
90-100	0	12 (13.48)	**41 (46.07)**	12 (13.48)	2 (2.25)
Post-Period					
70-80	0	0	1 (1.12)	0	0
80-90	0	0	1 (1.12)	0	0
90-100	0	13 (14.61)	**57 (64.04)**	15 (16.85)	2 (2.25)
Cholesterol					
Pre-Period					
50-60	0	2 (2.60)	1 (1.30)	0	0
60-70	0	0	1 (1.30)	1 (1.30)	0
70-80	0	0	2 (2.60)	0	0
80-90	0	4 (5.19)	5 (6.49)	1 (1.30)	1 (1.30)
90-100	0	13 (16.88)	**39 (50.65)**	7 (9.09)	0
Post-Period					
70-80	0	1 (1.30)	0	0	0
80-90	0	1 (1.30)	1 (1.30)	0	0
90-100	0	17 (22.08)	**47 (61.04)**	9 (11.69)	1 (1.30)

Comparing PDC values between the pre-period and post-period

The objective for this study was to compare the mean PDC values of the patients in pre-period with their PDC value in the post-period.

Wilcoxon Signed-Rank Test: PDC values were calculated for the pre-period and post period for each patient. A variable was created by subtracting the post-period PDC values from the pre-period PDC values for each patient. Considering the paired nature of the observations and non-normality of the PDC scores (proportion), a Wilcoxon Signed-Rank Test for paired data (*alpha= 0.05*) was performed separately for each of the drug categories.

Diabetes: An average PDC of 94 ± 0.14 and 99 ± 0.03 was found in the pre-period and post-period respectively. As a result of this analysis, a Wilcoxon-Signed Rank Test statistic of 143 (*p= 0.0001*) was obtained. The required sample size for this analysis was 82 patients whereas the current study had only 56 patients. Therefore sample size requirements were not met for this test.

Hypertension: An average PDC of 94 ± 0.12 and 99 ± 0.03 was found in the pre-period and post-period respectively. As a result of this analysis, a Wilcoxon-signed rank test statistic of 391 (*p= <.0001*) was obtained.

Cholesterol: An average PDC of 94 ± 0.11 and 99 ± 0.04 was found in the pre-period and post-period respectively. As a result of this analysis, a Wilcoxon-signed rank test statistic of 369.5 (*p= <.0001*) was obtained. The required sample size for this analysis was 82 patients whereas the current study had only 77 patients. Therefore sample size requirements were not met for this test.

The two-tailed p-values generated by the Wilcoxon-Signed Rank Test for each of the three drug categories was less than 0.05. Therefore, the null hypothesis was rejected and it is

concluded that statistically significant differences exist between the PDC values in pre-period and PDC values of post-period for all the drug categories. Results of this analysis are shown in detail in Table 7.

Table 7: Wilcoxon-Signed Rank Test Results

Drug Class	*Pre-Period* *Mean (Standard Deviation)*	*Post-Period* *Mean (Standard Deviation)*	*Wilcoxon-Signed Rank Statistic (S)*	*P (Two-tailed)*
Diabetes	0.94 (0.14)	0.99 (0.03)	143	0.0001*
Hypertension	0.94 (0.12)	0.99 (0.03)	391	<.0001*
Cholesterol	0.94 (0.11)	0.99 (0.04)	369.5	<.0001*

*Significant at $\alpha = 0.05$

Comparison between proportions of adherent patients in pre-period and post period

In a secondary analysis, the proportion of adherent patients in pre-period was compared to the proportion of adherent patients in post-period. Adherent patients were those who had a PDC value greater than or equal to 0.80 and were flagged as '1' and non-adherent patients were flagged as '0'. In order to calculate this proportion, the numerator included all those patients meeting the inclusion/exclusion criteria and flagged as "1". Whereas, the denominator included

all those patients meeting the inclusion/exclusion criterions and flagged as "1" or "0" both. In order to meet this research objective, McNemar's Exact Test was performed separately for each of the drug categories.

A McNemar's Exact Test was conducted rather than the original McNemar's Test to account for the small sample size employed in the study. This was also done keeping in mind that, the sum of discordant pairs in all the drug categories were less than 25 i.e. $b+c< 25$. A 2x2 contingency table was obtained as a result of this analysis and odds ratios with confidence intervals ranging from 5% to 95% were also obtained. Odds ratio results signified the odds of adherence (depending upon the drug class) in post-period as compared with pre-period. McNemar's Exact Test results are described below by drug category.

Diabetes: The required sample size for this analysis was 109 patients whereas the current study had only 56 patients, therefore, sample size requirements were not met. The results of 2x2 contingency table after performing the McNemar's Exact Test (Table 4) suggests that there were 51 (91.07%) adherent patients in pre-period whereas there were 56 (100%) adherent patients post-period. The test performed also yielded an exact p-value equal to 0.0625, greater than alpha 0.05. Using the results, the null hypothesis is not rejected. Therefore it can be concluded that although there was an increase in the proportion of adherent patients from pre-period to post-period, the difference in the proportion was not statistically significant.

The odds ratio of being adherent in post period as compared to pre-period was equal to infinity. This can be attributed to the fact that no one who was adherent in the pre-period stayed non-adherent in the post-period and no one who was adherent in pre-period became non-adherent in the post-period. In this situation one of the discordant pairs was zero, leading to an odds ratio equal to infinity. The odds ratio of infinity has a 95% CI ranging from 0.05 to infinity because in

a case when OR equal to infinity, the upper exact confidence limit is set to infinity and the lower limit is set to alpha, which is 0.05 for the current study. Therefore it can be concluded that there was large difference between the proportions of adherent patients in post-period as compared pre-period, however the difference was not statistically significant. Results of McNemar's Exact Test for diabetes drug category is shown in Tables 8 and 11.

Table 8: 2x2 Contingency Table for Diabetes

	Post-Period	
Pre-Period	Non-Adherent (%)	Adherent (%)
Non-Adherent	0	5 (8.93)
Adherent	0	51 (91.07)

Hypertension: The required sample size for this analysis was 95 patients whereas the current study had only 89 patients, therefore sample size requirements were not met. A total of 80 (89.89%) patients were adherent in the pre-period as compared to 88 (98.88%) patients in the post-period. The test performed yielded an exact p-value of 0.0215, less than alpha 0.05. Using these results, the null hypothesis is rejected and it is concluded that the difference in the proportion of adherent patients in pre-period and post-period is statistically significant.

When evaluating the odds of adherence, patients in the post-period had a 9 times higher odds of adherence as compared to pre-period. Results of the McNemar's Exact Test for the hypertension drug category is shown in Tables 9 and 11.

Table 9: 2x2 Contingency Table for Hypertension

	Post-Period	
Pre-Period	Non-Adherent (%)	Adherent (%)
Non-Adherent	0	9 (10.11)
Adherent	1 (1.12)	79 (88.76)

Cholesterol: A total of 70 (90.91%) patients were adherent in the pre-period as compared to 76 (98.70%) patients in the post-period. The test performed yielded an exact p-value equal to 0.0703 greater than alpha 0.05. Using the results, the null hypothesis is not rejected. Therefore it is concluded that although there was an increase in the proportion of adherent patients from pre-period to post-period, the difference in the proportion was not statistically significant.

When evaluating odds of adherence, patients in the post-period had a 7 times higher odds of adherence compared to the pre-period. Results of the McNemar's Exact Test for the cholesterol drug category is shown in Tables 10 and 11.

Table 10: 2x2 Contingency Table for Cholesterol

	Post-Period	
Pre-Period	Non-Adherent (%)	Adherent (%)
Non-Adherent	0	7 (9.09)
Adherent	1 (1.30)	69 (89.61)

In the pre-period, approximately 89.89% to 91.07% patients were considered adherent depending upon the drug category. Whereas, the proportion of adherent patients ranged from 98.70% to 100% in the post period depending upon the drug category. Table 8 contains all the results derived from the McNemar's Exact Test for all the three drug categories.

Table 11. Results of McNemar's Exact Test

	Adherent Patients (%)					
Drug Class	*Pre-Period*	*Post-Period*	*Odds Ratio (CI)*	*Change in Proportion*	*DF*	*P (Two-Tailed)*
Diabetes	51 (91.07)	56 (100)	0.05-Infinity	8.93	1	0.0625
Hypertension	80 (89.89)	88 (98.88)	9 (1.14-71.04)	8.99	1	0.0215*
Cholesterol	70 (90.91)	76 (98.70)	7 (0.86-56.89)	7.79	1	0.0703

*Significant at $\alpha = 0.05$

CHAPTER V

DISCUSSION

This study aimed to explain the impact of medication synchronization (med sync) on medication adherence. Adherence plays a crucial role in the Centers for Medicare and Medicaid Services' (CMS) Star Rating System which is designed to assist Medicare beneficiaries in plan selection. Among the five measures used by CMS and Pharmacy Quality Alliance (PQA) for calculating the Star Rating, three of them are related to the medication adherence.[3,7] From a clinical perspective, adherence is vital to attain the therapeutic effect of medication therapy, so it is critical to understand the importance of med sync program in improving the medication adherence of patients.

A quasi-experimental pre-post study design was employed for this study using pharmacy prescription fill data from various independent community pharmacies located in different regions of Mississippi. Patients were compared on the main outcome measure, medication adherence, before and after the medication synchronization intervention. Because this study employed a pre-post study design, patients served as their own control. Drug classes in the CMS Five-Star Quality Rating System that were examined include *oral diabetes medications, hypertension medications and cholesterol medications*. Data was utilized from three different pharmacies located in different regions of Mississippi.

Discussion of findings

The only demographic information available for patients in this study was age. Most patients were between 60 and 80 years old. Similar age trends were noted in an evaluation of another med sync program conducted by Holdford et al.[1] This is in line with the expectation that

older patients utilize more prescription medications than younger patients, and therefore are potentially better candidates for a med sync program.[27]

Because average PDC values in the post-period were higher than average PDC values in the pre-period, it is evident that the medication adherence improved after being enrolled in the med sync program. After performing Wilcoxon Signed-Rank Tests, it was found that the improved adherence was statistically significant in all three drug categories. It is worth noting here, however, that pre-period adherence values were exceptionally higher than the investigators expected. For example, average pre-period PDCs for all drug categories was 0.94, increasing to 0.99 after med sync was implemented. It is possible that patients who were most adherent, and thus being more present in the pharmacy for their refills and engaged in their own care, were not only perceived as needing med sync more, but also easier to recruit into the program, thus resulting in self-selection bias into the med sync program. Meaning that, patients in this study may not have been representative of typical patients in each of these pharmacies.

After finding that the PDC values between the pre-period and post-period significantly improved, a follow up analysis was conducted to confirm these findings. For this purpose, the proportion of adherent ($PDC \geq 0.80$) patients in the pre-period and post-period was calculated. Upon the formulation of a 2x2 contingency table the McNemar's Exact Test for small sample sizes (where the sum of discordant pairs were less than 25) was performed. For *oral diabetes medications*, an increase of approximately 8.93% adherent patients from pre-period to post-period was noticed. However, this increase in the proportion of adherent patients was not statistically significant.

Lack of a statistically significant change could be attributed to the small sample size for this drug category and presence of too much 'noise' in the data. The small sample for this study

can be explained by the fact that our sample largely consisted of adults between 60 and 80 years of age. In fact, four out of 56 in the diabetes medication category were between 80 and 100 years old. It is likely that older diabetes patients are being treated with insulin after first-line oral diabetic treatments used in the earlier stages of their disease. From a clinically practical standpoint, however, it is impressive to note that 91% of patients were considered adherent prior to the intervention, while 100% were considered adherence after the intervention. So while not a statistically significant change, adherence in more than 100% of patients cannot be obtained. Again, the fact that 91% of patients were adherent prior to the intervention may be reflective of a biased sample.

In the *hypertension* category, there were 80 (89.89%) adherent patients in the pre-period whereas there were 88 (98.88%) adherent patients post-period. As consistent with the direction of the previously stated hypothesis, an increase of approximately 8.99% adherent patients from pre-period to post-period was noticed. Despite a small sample and underpowered test, statistically significant improvements were still detected.

As with diabetes medications, the increase in the proportion of patients adherent to *cholesterol medications* was not statistically significant. Looking again from a clinical perspective, nearly 91% of patients were considered adherent prior to the intervention, while nearly 99% were considered adherence after the intervention. So again, while not a statistically significant change, practically speaking, having nearly 99% of patients adherent to their cholesterol medications is would be all accounts be considered reasonable in the practice setting.

Limitations

The study contains several limitations. The findings of current study may not be generalizable to a national population considering that this data was acquired from community

pharmacies located in Mississippi. The literature suggests that pharmacists can influence medication adherence, and each pharmacy will likely have its own impact on medication adherence, which was not controlled in this study.[1] The study also did not control for risk factors impacting adherence such as general comorbidities of patients, individual risk factors associated with respective drug categories, health insurance status, race, gender, severity of disease conditions, patients' motivation to be enrolled in med sync. Also, the findings from the current study will merely reflect the association between adherence and med sync and does not imply causality.

We were unable to identify exact index dates for each patients due to documentation issues in the pharmacies. Therefore, an estimate of the index dates was taken using available information such as enrollment dates and monthly prescription dispense dates. An algorithm for index date selection was used, such that the index date was the date after the enrollment date upon which the patient received multiple monthly prescriptions on the same date for at least three months.

Sample size requirements were not met for the diabetes and hypertension drug categories for McNemar's Exact Tests and sample size requirements were not met for diabetes and cholesterol drug categories for the Wilcoxon Signed-Rank Tests, making these tests underpowered. Upon discussion with the pharmacists, it was found that the med sync program offered in the pharmacies was an opt-in program in which the patients must consent to be enrolled in the program once the offer to join the program is made by the pharmacist. This can lead to self-selection bias because patients in the med sync program might be more engaged in their own health relative to other patients who chose not to enroll in the program. Not surprisingly, upon conversations with pharmacists, it was found that patients visiting the

pharmacy multiple times a month for refills were considered the best candidate for med sync. Although recruiting these patients is consistent with the objectives of med sync, simultaneously, it also creates a pharmacy-selected pool of patients who are highly enthusiastic about maintaining their health leading to a possible bias in the study.

Another challenge in this study was that, each of the pharmacies had different types of pharmacy management software which can lead to discrepancies in the data overall. Also, using PDC as an adherence measure assumes that if medication is possessed, it is consumed as well. In reality, this might not be the case. Additionally, patients who were excluded from the study due to a 90 day or more gap between fills might have not actually been non-persistent, but instead might have switched pharmacies or been advised by the prescriber to discontinue taking their medication. Considering the nature of the study as well as the nature of the pharmacy prescription transaction data used, it was outside the scope of this study to address these latter limitations.

Directions for future research

This study evaluated how med sync can potentially improve medication adherence of patients by employing a quasi-experimental pre-post study design by utilizing pharmacy prescription transaction data collected from independent communities situated in various regions of Mississippi. Moving forward, studies evaluating similar objectives should employ a randomized case control design. This will help to control for the self-selection bias that can occur when patients are approached about enrollment in med sync. Self-selection bias can lead to the enrollment of those patients who were motivated to improve their adherence already and can result in inflated PDC results both before and after a med sync intervention.

Also, considering the nature of prescription transaction data and the unavailability of the important risk factors that need to be controlled, a survey research could be used to supplement the secondary data evaluation of med sync on medication adherence. This may help researchers extract valuable information from the patients which is otherwise difficult to obtain from a pharmacy dispensing database.

Researchers conducting similar studies in the future should ensure consistent, controlled, and structured med sync programs. In particular there should be adequate and accurate documentation. Ideally, a dedicated researcher proficient with the process of medication synchronization should be appointed in the pharmacy to manage the program. Creating a comprehensive documents containing the guidelines to conduct med sync program should be created and should be followed strictly while implementing the program. Most importantly, future researchers should assure that med sync programs are adjusting refills based on patient-reported adherence, not just refilling a month's worth medication, assuming that they patient has been perfectly adherent. Doing the latter results in inflated adherence rating, and may be considered fraud by stakeholders reimbursing pharmacists for good adherence rates.

The convenience that comes with med sync for pharmacy patients is a relatively unexplored area. Not only are patients profoundly reducing the number of visits they make to the pharmacy, but their medication is already available in the pharmacy when they visit. Most importantly, med sync should allow for increased pharmacist contact and attention due to streamlined workflow. In theory, it can be assumed that all of this would lead to patient satisfaction. Future studies should aim at exploring such non-clinical benefits, or even health-related quality of life as a result of the med sync. These kind of assessments are of utmost

importance for third parties who may be paying pharmacists for such interventions and to maintain emphasis on a patient centric model.

Better inventory management, streamlined work flow, and less walk-in traffic are some of the benefits that a pharmacy receives when practicing med sync program. Considering that the pharmacist has a critical role to play in the program, the attitudes and satisfaction level of the pharmacist derived from a med sync program should also be assessed in future studies.

With scheduled monthly visits by the patients purchasing multiple prescription medications for the month, there is an expected increase in the revenue for the pharmacy. At the same time, there in a decrease in the overall walk-in visits which might would lead to a decrease in the upfront sales. A study in the future, evaluating the net benefit of this program might would help the pharmacy to understand med sync benefits from a monetary perspective.

Upon discussion with the pharmacist, it was found that pharmacies adjust the upcoming prescription's days of supply if a patient has not been adherent in the previous month or have missed few doses. Although they pay the same amount of co-pay associated with the drug they sometimes receive lesser quantity of doses depending upon their consumption in the last month. Some patients were not in favor of this and left the program because they did not wish to pay the same amount of co-pay and receive lesser drug quantity. From this we can infer that co-pay or co-insurance has an important role to play in the med sync program, therefore future studies should aim at exploring this issue in detail.

In exploring the core issue of the current study, improving adherence is most salient to stakeholders of med sync, particularly payers. There is a wealth of literature demonstrating positive intermediate and other clinical outcomes as a function of medication adherence. Linking improved adherence as a result of med sync with health outcomes should be a priority of future

med sync research, and will inevitably become a necessity for payers considering reimbursing pharmacies for such services. In addition to linking med sync to health-related outcomes, research should attempt to link med sync with health costs related to emergency room visits or hospitalizations. A detailed cost analysis could be performed by linking synchronized patients to Medicaid and other claims databases.

Conclusion

This is the first study to assess the impact of medication synchronization on medication adherence while employing a quasi-experimental pre-post study design by utilizing the pharmacy prescription transaction data from various independent community pharmacies in Mississippi. The results indicated that after being enrolled in med sync, medication adherence generally improves. When linked to literature that correlates adherence with positive health and economic outcomes, med sync programs can offer potential benefit to the healthcare system.

An important stakeholder in med sync is Centers of Medicare and Medicaid Services' (CMS) because they evaluate Medicare Part D plans on the basis of Star Rating system which is useful in making quality based payments to Medicare Advantage Plans (MA-PDs), selling benefits of prescription drug plans (PDPs) and assisting Medicare beneficiaries in plan selection. Results of this study and similar ones conducted in future will become even more important with the boom of commercial Part D plans making it necessary to monitor the adherence and subsequent health outcomes.

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- **Clinical Programmer**, *Accenture India Pvt. Ltd., Mumbai, India*. (July 2012 - July 2013)
    - Demonstrated good understanding of the clinical domain and expertise in analyzing and reporting of Phase I clinical trial data
    - Developed complex and reusable macros and extensively used existing macros and developed SAS programs for data cleaning, validation and report generation
    - Developed reports including tables and listings for inclusion in clinical study reports and regulatory submissions
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- **SAS Trainer**, *Unify Concepts, New Delhi, India.* (August 2011 - July 2012)
    - Responsible for training a group of students on Base SAS preparation and examination
    - Designed and conducted mock exams to enhance their skills and knowledge
    - Provided timely feedback to the students to enhance their learning

COURSEWORK:

- Research Methods ● Primary Data Techniques ● Secondary Data Techniques ● Quantitative Methods in Psychology ● General Linear Models ● Applied Multivariate Analysis ● Data Management and Statistical Software ● Pharmacoeconomics ● Health Economics ● Pharmaceutical and Healthcare Policy ● Drug Development and Marketing
- *Independent Study*: "Assessing medication adherence towards mercaptopurine among children suffering from Acute Lymphoblastic Leukemia (ALL) in a national sample of 36 states' Medicaid data in the U.S."

RESEARCH INTERESTS:

- Health Outcomes Research ● Patient Reported Outcomes ● Clinical Research ● Pharmacoeconomics ● Medication Adherence ● Health Economics ● Secondary Database Analysis Research ● Big Data Analytics ● Health-Related Quality of Life ● Decision Modelling

RESEARCH SKILLS:

- Certified Base Programmer for **SAS® 9.0**
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- Elementary knowledge of UNIX operating system
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TRAINING COURSES:

- Introduction to Pharmacoeconomics, International Society of Pharmacoeconomics and Outcomes Research (ISPOR)
- Introduction to Outcomes Research, International Society of Pharmacoeconomics and Outcomes Research (ISPOR)
- Distant learning course from World Intellectual Property Organization (WIPO) titled "General Course on Intellectual property"

PRESENTATIONS:

- **Verma D**, Banahan III B, Hardwick SP, Clark JP. Developing algorithms for identifying beneficiaries with higher than expected utilization of opioids analgesics. International Society of Pharmacoeconomics and Outcomes Research (ISPOR) – 20th Annual International Meeting, Philadelphia, PA. (May 2015)
- **Verma D**, Yang Y, Bowlin EM. A Markov cost-effectiveness model comparing fluticasone propionate/salmeterol combination (SFC) and mometasone furoate/formoterol fumarate dehydrate (MF) in the management of asthma. International Society of Pharmacoeconomics and Outcomes Research (ISPOR) – 19th Annual International Meeting, Montreal, QC, Canada. (June 2014)

MASTER'S THESIS:

- "Impact of refill synchronization on medication adherence for chronic diseases" (December 2015)

CLASS PROJECTS:

- *Health Economics*: "Impact of attention deficit hyperactivity disorder (ADHD) and its treatment on missed school days among school going children (5-17 years) in United States using MEPS database"
- *Pharmaceutical and Healthcare Policy:* "Medication synchronization using appointment based model—A commentary"

- *Pharmacoeconomics*: ”A Markov cost-effectiveness model comparing fluticasone propionate/salmeterol combination (SFC) and mometasone furoate/formoterol fumarate dehydrate (MF) in the management of asthma”
- *Primary Data Techniques*: “Perceptions of employees on expanding employee health services at the university” -- Focus groups and questionnaire development
- *Research Methods*: “Short term impact of environmental supports (CAT, GES, and Pharm-CAT) on cognitive functioning and medication adherence in outpatients with schizophrenia: A proposal”
- *Secondary Data Techniques*: “Developing algorithms for identifying beneficiaries with higher than expected utilization of opioid analgesics -- Mississippi Medicaid Database”

AWARDS:

- University of Mississippi Graduate School Travel Grant for attending the ISPOR 19th Annual International Meeting, Montreal, QC, Canada, June, 2014
- University of Mississippi Graduate School Travel Grant for attending the ISPOR 20th Annual International Meeting, Philadelphia, PA, May, 2015

SERVICE:

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