The Effect of Patient-centered Prescription Drug Labeling on Medication Adherence among Wisconsin Medicaid Enrollees

By

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DISCLAIMER

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ABSTRACT

Up to 50% of patients have difficulties understanding instructions on prescription drug labels. This can result in medication nonadherence, and downstream poor clinical outcomes and avoidable healthcare use and cost. Patient-centered prescription drug labeling (PCL) is a strategy to enhance clarity and readability of prescription drug labels that are affixed to prescription drug containers at the time of dispensing from a pharmacy. Common components of PCL include the use of larger font, highlighted text, additional white space, simple language, and prioritization and logical organization of important information to facilitate patient understanding of medication instructions. Following PCL guidelines contained in the US Pharmacopeia Chapter 17, between late 2016 and 2018, with the support from Wisconsin Health Literacy, 63 pharmacy locations in Wisconsin re-designed the label attached to dispensed medications. The goal of the PCL re-design was to improve patient understanding of medication use and medication adherence. Objectives of this current study are to evaluate the effect of this PCL re-design on medication adherence to chronic medications and to investigate the heterogeneous effect of PCL on medication adherence by baseline medication adherence and regimen complexity.

A pre-post quasi experimental, non-equivalent control group design was used to examine the impact of the PCL on medication adherence to chronic medications among Wisconsin Medicaid enrollees. The treatment group contains medications that were dispensed to Medicaid enrollees from one of the 63 participating pharmacies after the PCL label was implemented. The control group includes medications dispensed to Medicaid enrollees from Wisconsin pharmacies that did not create a PCL. Data for this evaluation were obtained from the University of Wisconsin Institute for Research on Poverty (IRP) and included Wisconsin Medicaid administrative enrollment records, pharmacy claims and medical encounter data. Ordinary least

squares regression analysis using a difference-in-difference approach was adopted for statistical modeling of the impact of the PCL on medication adherence, measured as the proportion of days covered (PDC).

Manuscript#1 evaluated the impact of the PCL on medication adherence. The results showed that the PCL improved average PDC by 1.17 percentage points in the treatment group relative to the control group. Sensitivity analyses using binary medication adherence measure (PDC ≥ 80%) indicated robust findings.

Manuscript#2 assessed the effects of the PCL on medication adherence for Medicaid enrollee medications stratified by baseline medication adherence level. For medications with the lowest 25% baseline medication adherence, the PCL significantly improved medication adherence for the treatment group by 2.19 percentage points relative to the control group. There were no significant changes in mean PDC between study groups for the stratum of medications with baseline medication adherence above the lowest 25%. Sensitivity analyses found consistent results.

Manuscript#3 evaluated the effects of the PCL on medication adherence by medication regimen complexity level, including the number of concurrent medications used, and the number of times per day a medication is to be taken. For enrollees taking five or fewer concurrent medications, the mean PDC significantly increased by 2.71 percentage points in the treatment group following PCL implementation relative to the control group. For medications that were taken once or fewer times daily, the mean PDC significantly increased by 1.34 percentage points after the PCL was implemented in the treatment group relative to the control group. Contrary to our hypotheses, there were no significant improvements in the mean PDC for other categories of higher regimen complexity level. Sensitivity analyses showed comparable results.

The PCL label implemented by some Wisconsin pharmacies significantly improved medication adherence among Medicaid enrollees who used medications to manage chronic conditions. The improvement in adherence was associated with low baseline adherence level and was not associated with high medication complexity level. Overall, the results add additional evidence that PCL may be an effective strategy to improve medication adherence among Medicaid enrollees.

DOCUMENT ORGANIZATION

The dissertation includes seven chapters. The first chapter introduces the patient-centered prescription drug label (PCL) interventions in Wisconsin and reviews relevant existing literatures. Chapter two describes the research objectives and hypothesis. Chapter three overviews the study design and methodology that were used for all three manuscripts. Chapter four, five and six each contains manuscript that addresses each of the three study objectives of the dissertation. Chapter four covers the overall effect of the PCL intervention on medication adherence among the Wisconsin Medicaid populations. Chapter five focuses on how PCL intervention may have differential effect medication adherence for enrollees with higher or lower baseline medication adherence. Chapter six explores the effect of PCL on medication adherence for enrollees with different level of medication regimen complexity. Lastly, chapter seven summarizes all findings from the dissertation and discusses implications and conclusions.

CHAPTER ONE: INTRODUCTION

1.1 Significance of Evaluating the Impact of Patient-centered Prescription Drug Label in Wisconsin

Poor understanding of prescription drug labels affixed to medication containers at pharmacies can lead to medication nonadherence, resulting in suboptimal treatment outcomes, and increased hospitalizations, health care costs, medication errors or adverse drug events.[1–6] Almost half of the patients are unable to correctly interpret prescription dosage instructions located on prescription labels.[7] This is especially common for patients with limited health literacy[7,8] which is often associated with disadvantaged socioeconomic status, being in a racial or ethnic minority group or having complex oral medication regimens.[7–9]

One potential strategy to improve patient understanding of prescription drug labels and medication adherence is through enhancing the clarity and readability of prescription drug labeling. In 2013, United State Pharmacopeia (USP) renewed a set of standards (see **Table 1.1**) for prescription drug labeling to promote patient understanding of prescription drug labels and safer medication use. Starting in 2014, Wisconsin Health Literacy (WHL) initiated a research project to assess whether these standards can be implemented in Wisconsin. The findings suggest while the awareness of these USP standards was low, pharmacists and software vendors were in support of adopting these standards. [10] Between 2016-2018, the new prescription drug label was successfully implemented in 5 pharmacy organizations with 63 pharmacy locations based on these USP standards. The design of the new label incorporated input obtained from the Project and Patient Advisory Councils. Each pharmacy organization also followed a different redesign process based on organizational structure and pharmacy software vendor.

Initial data from one study pharmacy organization showed improvement in medication adherence measured by medication possession ratio (MPR) before and after the label change.[11,12] However, the finding is based on 288 patients covered by Children's Community Health Plan and without a comparison group. Such single group design may be susceptible to threats to internal validity due to maturation and history. Additionally, only a few studies investigated the effectiveness of PCL that incorporates the Universal Medication Schedule (UMS) or USP standards. Although studies showed that a PCL improved patient's understanding of medication instructions,[9,13–16] the findings about its impact on medication adherence are inconclusive.[17–22] As such, the overall effect of PCL in Wisconsin remains unclear**. Research to evaluate the effects of the PCL by expanding the sample size of patients impacted by the PCL and improving the study design by including a control group of patients not exposed to the PCL is needed.**

Further, previous research found certain patient characteristics such as low health literacy and having complex treatment regimens including multiple concurrent medications and frequent dosing schedules are associated with poor understanding of prescription drug instruction and low medication adherence.[7–9,23] These characteristics are commonly seen among Medicaid enrollees, a population with a relatively low socioeconomic status (SES), and a high prevalence of chronic disease, multiple drug use and medication nonadherence.[24,25] One study found that a health literacy intervention may be more beneficial for those with lower medication adherence.[26] However, no previous study has assessed the effect of PCL on a Medicaid population and whether individuals with lower baseline medication adherence can benefit more from the PCL. Furthermore, the effect of PCL across different regimen complexity levels has not been systematically studied. Only one study explored the effect of PCL in a subset of patients with multiple medications[18] and only two studies targeted patients using medication with more frequent dosing schedules. [21,22] The results suggest label improvement interventions improved medication adherence among those with a more complex medication regimen. **Therefore, further research is needed to study the effect of PCL among the Medicaid population as well as by their baseline adherence level, number of concurrent medications, and medications with frequent dosing schedules.**

We hypothesize that the label change intervention can benefit the Medicaid enrollees, a population in which low socioeconomic status, low health literacy,[27] chronic diseases and comorbidities,[24] multiple drug use and non-adherence [25] are common. Given that no previous studies have examined the impact of a PCL using prescription claims data from a state Medicaid program, it is unknown whether the PCL intervention is effective at improving medication adherence for this population with a disproportionately higher risk of medication nonadherence. To better understand the effect of PCL, the objectives of this study are to examine the effect of PCL on medication adherence among Medicaid enrollees 1) by baseline medication adherence, 2) by the number of concurrent medications used and 3) by the frequency of medication dosing schedule.

1.2 Literature Review

1.2.1 Poor Understanding of Prescription Drug Instructions

Patient misunderstanding of instructions on prescription drug labels is common and can lead to severe consequences. Up to 50% of patients with chronic diseases have difficulties understanding the instructions on the prescription labels attached to the drug containers. [7] This can cause subsequent medication nonadherence,[14] which is associated with an increase in hospitalization risk, mortality and medical spending among patients with chronic disease.[4,28,29]

An estimate of 125,000 avoidable deaths and $100 billion in preventable medical cost is attributable to medication non-adherence.[30]

One root cause of poor patient comprehension and subsequent medication nonadherence is poor prescription drug labeling. [13,14] Under the circumstances when the communication of medical-related information between patients and providers is ineffective and suboptimal, [31–33] patients often rely on the prescription drug labels affixed to the drug container for guidance in taking their medications.[34] Although prescription drug labels may appear to be straightforward, they are not always clear to patients. There can be considerable variability in the wording of the instructions, use of icons and the format of labels.[8,35] For example, one study found that missed or unclear information is common when physician prescriptions were transcribed by the pharmacist into labels on the drug containers, with 2% omitting dosing frequency, 98% using implicit timing instruction and 50% missing auxiliary instructions.[36] In another study by Davis and colleagues, it was found that even though the majority of patients could correctly state they would take two pills two times per day for medicines instructed as "*take two tablets by mouth twice daily*", approximately 70% failed to demonstrate what the instruction meant by counting out 4 tablets to be taken per day.[37]

Patient health literacy is another factor negatively associated with patient comprehension of how to take medications.[7,8,38–40] Personal health literacy was defined as "the degree to which individuals have the ability to find, understand, and use information and services to inform health-related decisions and actions for themselves and others." in Health People 2030. [41] While the relationship between health literacy and medication adherence is inconclusive,[42,43] health literacy was found to affect medication adherence through reading drug labels and understanding prescription instructions.[44] Studies showed that patients with low health literacy were approximately three times more likely to misinterpret prescription drug labels.[7,14] Among patients with low health literacy, the complexity of instructions, clarity of label language, explicit statements of dosage interval and timing, use of unfamiliar terms or use of confusing icons are common drivers of misunderstanding.[8,38]

1.2.2 Patient-Centered Prescription Drug Labeling

To address the issue with the misunderstanding of prescription drug labels, several efforts have been made to provide guidance on what and how information should be presented on the prescription drug label. In 2008, IOM issued a call for an evidence-based approach to standardizing prescription drug labels.[34] Based on findings of a systematic review, the report suggests the use of larger fonts, the use of lists, headers and white spaces for readability reasons; the content should be written in simple language with information logically organized in an easily comprehensive manner.[45] The concept of UMS was also introduced in the IOM report and was later recommended as best practice to convey simplified dosage instructions for both patients and their caregivers by the American College of Physicians Foundation. The UMS provides explicit timing for taking medication in the wording of dosage instructions by categorizing and specifying dosage intervals into only four time period: “morning, noon, evening or bedtime”. It also uses numerals (“1” instead of “one”) and simple languages (“pill” instead of “tablet”) to improve readability and patient comprehension of labeling instructions. [22]

UMS and its variants, which often contain additional content and format optimization based on patients’ inputs, are commonly referred to as PCL. In 2012, both were endorsed by the USP Chapter 17 for prescription labeling on drug containers dispensed by pharmacists.[46] The recommendations incorporate the UMS principles and other formatting and information organizing considerations, including emphasizing instructions and other information important to patients, providing the purpose of use, and addressing comprehension issues for those with limited English proficiency and visual impairment.

Table 1.1 Common terms to describe standardized labeling strategy

Standardized label strategy	**Descriptions**	**Components**
Universal Medication Schedule (UMS) [22,47,48]	UMS is a methodology developed by National Council for Prescription Drug Programs (NCPDP) that uses simplified language for medication administration instructions. The goal of UMS is to increase patient understanding and adherence to medication instructions by standardizing the phrasing of directions, thereby improving health outcomes.	Provide explicit timing with standard intervals (morning, noon, evening, bedtime) for drug dosing; use numerals (“1” instead of “one”) and simple languages (“pill” instead of “tablet”) in the dosing instruction.
Patient-centered prescription drug labeling (PCL)[21]	PCL is a broad term to describe a labeling strategy that uses an evidence-based approach for format and content and often contains instructions conveyed with UMS.	PCL often contains prioritized information, larger font size, and increased white space. It often contains instructions that use UMS.
USP standards [46]	It is one form of PCL with a set of recommendations developed by the U.S. Pharmacopeial Convention in 201 that can be applied to the format, appearance, content, and language of prescription container labeling. The goal is to promote patient understanding by assisting physicians and pharmacists to provide patients with essential information needed.	Organize the prescription label in a patient-centered manner; emphasize instructions and other information important to patients; use simplified and concise language; give explicit instructions; include the purpose for use; limit auxiliary information; address limited English proficiency when possible; improve label readability; address visual impairment by providing alternative-access methods

Most studies have shown a positive impact of the prescription labeling standards on improving patient understanding of medication dosage instructions. [9,13–16] PCL instructions were 30% more likely to be interpreted correctly compared to standard instructions. Patients with limited health literacy were more likely to correctly interpret PCL instructions relative to non-PCL instructions.[49] Use of explicit dosage instruction with specific times or time periods was more likely to be understood by patients compared to instructions stating times per day.[14] Another study found that a PCL strategy improved patient's understanding of prescription instructions and increased the likelihood of both correct medication use (including dose, frequency and spacing) and consolidation of medications (reducing the number of distinct times medications were taken each day) for a multi-drug regimen. [13]

1.2.3 Medicaid Enrollees and Medication Adherence

Medicaid enrollees are disproportionately at greater risk of misunderstanding prescription drug labels and subsequently, at greater risk of having worse medication adherence. [50–52] The Medicaid population is composed of a low-income population that has a higher proportion of racial minorities. Approximately 60% of Medicaid enrollees are racial or ethnic minority groups (about 20% African Americans, 25% Hispanics and 15% other races or ethnicities), [53] which is disproportionately higher than the national average of 40% non-white or Hispanic (13% African American, 18% Hispanics, and 10% other races or ethnicities).[54] The Medicaid population also is prone to have basic or below basic health literacy [55] and a high prevalence of comorbidities. [24]

These characteristics commonly seen among Medicaid enrollees have been previously found to be correlated with medication nonadherence, [25,56–59] with health literacy playing an intermediate factor that explains how racial and SES characteristics may have affected medication adherence. Studies found an average lower medication adherence rate in geographic areas segregated with racial minorities and areas characterized as low income. [56,57] Lower health literacy is more prevalent among people living below the poverty level and among racial and ethnic minorities[60,61] and explains some of the racial disparities in medication adherence [62] and the SES disparities in health-related outcomes. [63] An inverse relationship between the number of comorbid conditions and medication adherence was also observed. [57,58] Therefore, given the characteristics of the Medicaid population, it is hypothesized that a PCL intervention may be potentially beneficial to this population in terms of enhancing patient understanding of instructions on prescription drug labels and improving their medication adherence.

1.2.4 Baseline Adherence

Medication adherence interventions may have heterogeneous effects across patients with different characteristics, including their baseline medication adherence levels.[64] Prior studies have found that individuals with lower baseline medication may be more responsive to an intervention designed to improve medication adherence or a change in policy that may improve medication adherence. [26,65,66] Other studies suggest individuals with higher medication adherence at baseline were more likely to show improvement post-intervention.[52,67] For example, one study found that an electronically delivered health literacy intervention was associated with a greater increase in medication adherence among patients with HIV who had a lower level of baseline medication adherence. [26] In contrast, another study of a motivational interviewing intervention led by student pharmacists found that higher medication adherence at baseline is associated with a greater increase in medication adherence after the intervention. [67] Whether a PCL will have a differential effect on patients with different levels of medication adherence at baseline is unclear and requires further research.

1.2.5 Complexity of Medication Regimen

Previous evidence suggests medication regimen complexity is associated with medication nonadherence. A systematic review and meta-analysis, using the Medication

Regimen Complexity Index (MCRI) which measures medication regimen complexity, found greater regimen complexity is associated with medication nonadherence (adjusted OR=1.05; 95% CI= 1.02-1.07).[68] In a systematic review using various medication regimen complexity measures, the majority of studies (35 out of 54) showed a negative relationship between regimen complexity and medication adherence. [23]

The complexity of a medication regimen is a concept without a universal measure and definition. Of the variety of measures, MRCI and Medication Complexity Index (MCI) are the most frequently utilized measurements to assess the regimen complexity of treatment across diseases. [23,69] Nevertheless, it is also common for studies to use their own unique measurement, with various interpretations and definitions of regimen complexity. Notably, regardless of the measurement, the most commonly seen components of the complexity measures were number of medications (95%) and administration frequency (95%). [69]

2.5.1 Multiple Medication Use

Multiple medication use is only one component of medication regimen complexity, yet it is the most used component and was found to be strongly correlated with medication regimen complexity. [69,70] The impact of multiple medication use on adherence to the treatment regimen is mixed. Previous studies showed that multiple medication use increased the risk of medication nonadherence.[71–73] For instance, one study found that, compared to patients with zero to one antihypertensive or lipid-lowering medications, patients with two medications, three to five medications, and/or six or more medications were 33%, 44% and 57% less likely, respectively, to be adherent to medications after other factors such as patient demographics, clinical characteristics, and health services use patterns were adjusted.[71] However, other studies found opposite or non-significant results.[74–76] For example, one study showed that patients having more than three cardiovascular medications were positively associated with medication adherence compared to patients with three or less medications. [74] Another study by Davis and colleagues found that taking 5 or more medications increased the risk of misunderstanding of medication instructions by almost three times (adjusted RR: 2.98, 95 %CI 1.40-6.34).[7] Given the common variation in the contents of prescription drug label instructions by type of medication, [35] patients with more prescribed medications likely experience a higher burden related to understanding medication instructions and managing their medication properly than those with fewer prescribed medications.

2.5.2 Frequent Daily Dosing

Administration frequency is another commonly used component to assess medication regimen complexity. Previous research suggests an inverse relationship between medication adherence and medication dosing schedule. [77–82] A meta-analysis of 51 studies assessed the effect of dosing frequency on adherence measured by electronic monitoring devices among patients with chronic disease. [77] The results found a significantly lower medication adherence among medications taken twice (-6.7%), 3 times (-13.5%) or 4 times (-19.2%) per day compared to medications taken 1 time per day. [77] Consistently, another meta-analysis by Srivastava et al [82] showed that once daily dosing schedules were 3 times more likely to have higher medication adherence compared to greater than once daily dosing schedules.[82] Similar results were found in one earlier meta-analysis of antihypertensive medications comparing once-daily dosing versus twice daily and multiple daily dosing.[80]

1.2.6 Studies Evaluating the Effect of Prescription Drug Label on Medication Adherence

Despite the positive effect of PCL on patient comprehension, the impact of PCL or UMS on medication adherence is less conclusive. Appendix A1 summarizes studies evaluating the impact of PCL or UMS on medication adherence. The study author, publication year, study design, patient population, the type of label change, adherence outcome and study findings are summarized in the table.

Six out of seven identified studies focused on patient populations with chronic disease(s) including diabetes (n=3), hypertension(n=1), coronary heart disease (n=1), and asthma (n=1) and one study examined older adults. For the adherence measure, 3 studies used subjective self-reported adherence and 4 studies used objective adherence measures including the proportion of days covered (PDC), MPR, or cumulative medication gap (CMG). Four studies with comparison (i.e., control) groups showed no difference in adherence between the treatment and the control(s) while three studies found improvement in adherence. Of the 3 studies showing improvement, 2 are pre-post pilot studies without a comparison group and 1 study used a comparison group but the effect size was relatively small.[28] Three studies which included a subgroup analysis conducted by Kripalani et al and Wolf et al showed PCL may benefit certain populations at greater risk of medication nonadherence, such as patients with multiple concurrent medications, those with frequent dosing schedules, those with limited literacy, and patients with less educational attainment. [18,21,22]

1.3 Gap in the Research

Findings from these studies are limited and several research gaps were identified:

1. While the preliminary results from the Wisconsin PCL showed an increase in populations with higher medication adherence measured by MPR, it was assessed within the treatment pharmacies before and after the label change with only 288 patients included. No formal evaluation with a stronger design has been conducted and the effect of

Wisconsin PCL remains unclear. To understand the effect of the Wisconsin statewide PCL, a study utilizing a pre-test – post-test, non-equivalent control group design and a longer study period is needed.

2. No previous studies known to the author explored the effect of PCL among Medicaid enrollees, a low-income population that has a disproportionately higher risk of medication nonadherence.
3. Results about the impact of PCL on medication adherence are mixed. Whether this is due to varied study populations, the type of prescription drug label improvement, the study design, or a short follow-up period is not clear. Although studies found that PCL may increase medication adherence among high-risk groups, the effect of PCL across patients with different levels of baseline adherence and regimen complexity was not systematically studied as most of the analyses are post-hoc, with limited sample size in the subgroups analyzed.
4. Most of the previous studies used either subjective self-reported or dichotomized objective medication adherence measures (i.e., PDC or MPR > 80% or CMG <20%), which can mask the effect of PCL on improving medication adherence among patients with adherence below subjective cut-off points (i.e., 80%).
5. Other limitations include small sample size, the inclusion of only prescriptions dispensed from one pharmacy network or one pharmacy corporation, [17,22] and not incorporating USP standards into the design of the PCL.

CHAPTER TWO: RESEARCH OBJECTIVES AND HYPOTHESIS

The evaluation of the prescription label change intervention will inform Medicaid programs about its ability to potentially improve medication adherence. The overall objective of the project will be addressed by the following specific aims:

Specific Aim 1: To evaluate the average treatment effect of PCL on improving medication adherence among Wisconsin Medicaid enrollees. (manuscript#1)

> We hypothesize PCL will improve medication adherence for Wisconsin Medicaid enrollees taking medications to manage chronic conditions.

Specific Aim 2: To evaluate the average treatment effect of PCL on Wisconsin Medicaid enrollees with low baseline adherence and enrollees with high baseline adherence. (manuscript#2)

> We hypothesize that the effect of PCL will be larger for enrollees with lower medication adherence before the PCL was used relative to enrollees with higher medication adherence before the PCL was used.

Specific Aim 3: To evaluate the average treatment effect of PCL on medication adherence across two dimensions of medication regimen complexity, the number of concurrent chronic medications taken and the times per day a medication was to be taken. (manuscript#3)

> We hypothesize the effect of the PCL will be larger for enrollees who were using more concurrent medications per day to manage chronic conditions relative to enrollees taking fewer concurrent medications per day. An additional study hypothesis is that the effect of the PCL will be larger for medications that are taken 3 or more times per day relative to medications that are taken 2 times per day and medications that are taken 1 or fewer time per day.

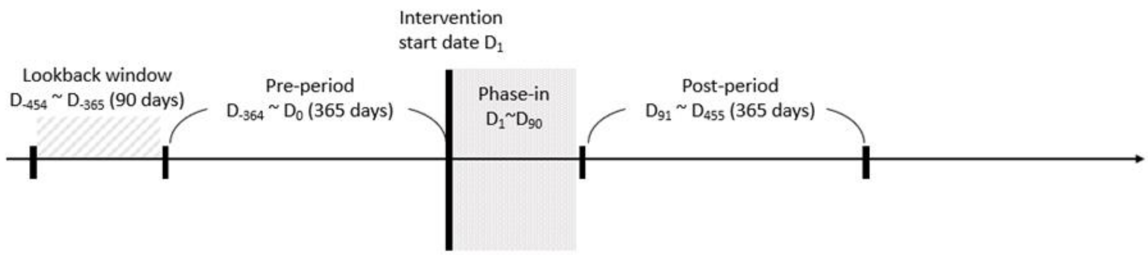
CHAPTER THREE: METHODS

This chapter summarizes the methodology that is applied to all three manuscripts. The first section describes the study design applied to the evaluation of the PCL effect on medication adherence. The second section covers the data sources used, including the Medicaid data files provided by the University of Wisconsin-Madison Institute for Research on Poverty (IRP), participating pharmacy data sources and other publicly available data sources. The third section provides details for sample identification processes and the last section includes the theoretical framework.

3.1 Study Setting and Design Overview

The study uses a pre-test–post-test, non-equivalent control group study design to estimate the effect of PCL on medication adherence with a difference-in-difference statistical analysis approach (**Figure 3.1**). Wisconsin Medicaid enrollment, medical claims and prescription drug claims data from January 2015 to December 2019 were used in combination with other pharmacy data files (See section 3.2 Data Sources). The study follows a set of inclusion and exclusion criteria and processes to identify the treatment and control medications (See Section 3.3 Sample Identification). The outcome variable, medication adherence, was measured by proportion of days covered (PDC), a common metric to calculate medication adherence that adjusted for medication oversupply (See Section 3.4 Medication Adherence).

Figure 3.1 Overview of study design

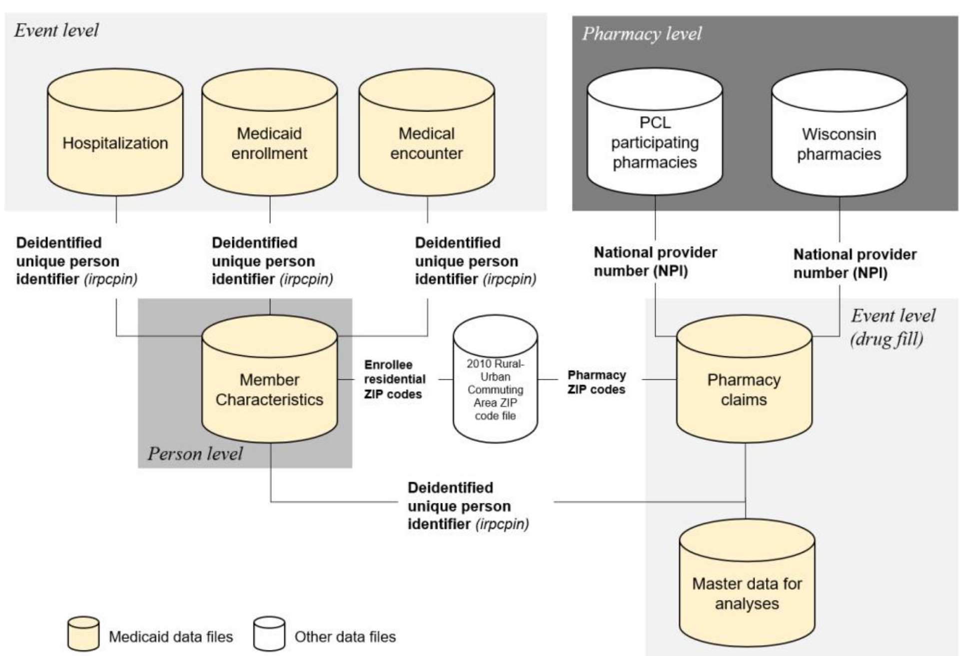


Notes: The pre-period was defined as 365 days before the PCL intervention start date. A 90-day phase-in period was included after PCL in which mediation adherence is not measured, followed by a 365-day post-period. A 90-day lookback window prior to the beginning of pre-period was also used to account for drug supply before the pre-period started to better estimate PDC.

3.2 Data Sources

In addition to the Medicaid data, several data sources were used and link to provide more information. **Figure 3.2** summarizes how different data segments were used and linked into the master data prepared for statistical analyses.

Figure 3.2 Construction of analytical data file



3.2.1 Medicaid Data Files

Separate Medicaid data files from the beginning of the year 2015 to the end of 2019 were obtained. Data files including the member characteristics file, Medicaid enrollment file, hospitalization file, medical encounter files (outpatient visit, emergency room visit and health maintenance organization visit) and pharmacy claims file were obtained from the IRP. We used the deidentified unique identifier (*irpcpin*), a number assigned to each Medicaid member, for the linkage of all the Medicaid data files.

The member characteristics file contains information for the Medicaid enrollees, including their birth date, race, ethnicity and residential 5-digit ZIP codes. The information was used to compute enrollees' age on the first day of the year 2015, which is the time when the study period started. Other member characteristics were used as covariates in the statistical analyses as indicated in Section 3.4. The Medicaid enrollment data contains each episode of enrollment from Medicaid plans during the study years whereas the hospitalization data contain the hospitalization record for Medicaid enrollees. To ensure the data completeness for PDC calculation, the enrollment and hospitalization data files were used to identify enrollees who were continuously enrolled in Medicaid each month and who were not hospitalized over 90 days as the study sample. The diagnosis ICD10 codes from medical encounters files were used to compute the Charlson Comorbidity Index, which was included as covariates in the statistical analysis.

Pharmacy claims data include records for each prescription drug fill for all Medicaid enrollees. Information on the prescription ingredient, the generic therapeutic classification system, the AHFS pharmacologic-Therapeutic Classification System, drug dosage form, route, billed date, total days supply and supply quantity, whether the drug is reimbursed by Medicare

Part D as well as information on the dispensed pharmacy, including the National Provider Identification (NPI) number, county and 5-digit ZIP codes of where the pharmacy was located, were recorded in the data.

3.2.2 Data Source of PCL and Wisconsin Pharmacies

Additional pharmacy data sources were used to provide more information on Wisconsin pharmacies that dispensed the prescription drug claims. First, a list of the PCL participating pharmacies was obtained from the Wisconsin Health Literacy (WHL). The dataset contains information on the pharmacy name, the NPI number and the PCL implementation start date. We linked the dataset to the Medicaid pharmacy claims data by the NPI number. Using this approach, we were able to identify medications that were dispensed from the pharmacy that implemented the PCL and further categorized these medications as those that were exposed to the PCL intervention. Second, we obtained a list of licensed pharmacies from the Wisconsin Department of Safety and Professional Services, which encompasses information on the NPI, provider name, and addresses of Wisconsin pharmacies. We linked the data to Medicaid claims data and were able to categorize the sample pharmacies into pharmacies that belong to a health system (a hospital, clinic or a provider network) or community pharmacies (chain or independent pharmacies) based on provider names. Lastly, we used the information available on the CMS National Plan and Provider Enumeration System (NPPES) NPI Registry [84] to cross-check if the NPI number of the PCL pharmacies was deactivated and changed at a certain time point during the study period. If this were the case, both the deactivated and the updated NPI numbers were used to ensure better categorization of the PCL exposure.

3.2.3 Other Publicly Available Data Sources

We obtained the 2010 Rural-Urban Commuting Area (RUCA) ZIP code file from the US Department of Agriculture Economic Research Service.[85] The file contains the zip codes and their corresponding primary and secondary rural-urban category. The RUCA codes group U.S. census tracts based on population density, urbanization, and daily commuting flow. This data file was used to link to the enrollee's residential ZIP codes and the pharmacy's ZIP codes. We combined the primary RUCA codes into four levels: metropolitan, micropolitan, small town, and rural commuting areas. The primary RUCA codes of where the pharmacy was located were used to choose the control pharmacies. We also used the primary RUCA codes of where the enrollee resides and where the pharmacy located as covariates in the statistical analysis.

3.3 Sample Identification

3.3.1 Determining Chronic Conditions

Adherence to long-term therapy is essential to reducing the risk of further complications, hospitalization events or death. [4,28,86] Thus, the study only included medication for treating or managing chronic conditions. We first identified the commonly prescribed therapeutical categories (> 5%) in the Medicaid pharmacy claims data. We then referenced previous research [87] and created a list of chronic conditions medications for treating or managing chronic conditions as listed in **Table 3.1**. AHFS Pharmacologic-Therapeutic Classification System codes recorded in the data were used to identify mediations of the listed therapeutic category. PDC, a preferred metric to calculate medication adherence for long-term therapy used by Pharmacy Quality Alliance (PQA)[88], was only calculated for medications that were for the therapeutic categories listed below.

Table 3.1 Medications for treating or managing chronic conditions

Chronic conditions	Therapeutic categories
ADHD	ADHD stimulant; ADHD, miscellaneous
Depression	Alpha2 receptor antagonist; Antidepressants cyclic Antidepressants, miscellaneous; MAOIs; Serotonin modulators; SNRIs; SSRIs
Diabetics	Biguanides; DDP4 inhibitors; Incretin Mimetics; Meglitinides; SG2 inhibitors; Sulfonylureas; Thiazolidinediones
Hyperlipidemia	Bile acid sequestrants; Cholesterol absorption inhibitors; Fibric acid derivatives; Statins
Hypertension	ACEIs; Alpha-blocker; ARBs; Beta-blocker; Calcium Channel Blocker; Renin inhibitor
Autoimmune disease	Anti-inflammatory agents (GI); Hormones - Adrenals DMARDS; Immunomodulatory agents
Other heart conditions	Antianginal agents (non-nitrate); Antiarrhythmics Antiplatelets; Non-warfarin anticoagulant
Dementia	Acetylcholinesterase inhibitors; NMDA receptor antagonists
Diuresis	Loop diuretics; Potassium sparing diuretics; Thiazide diuretics; Thiazide-like diuretics
Gout	Antiarthritics
Osteoporosis	Bisphosphonate Hormones-Estrogens Vitamin D
Other mental health	Antimanic agents Antipsychotics-First generation Antipsychotics-Second generation
Parkinson's disease	Antiparkinsonian Agents
Peptic ulcer	Proton Pump Inhibitor
Seizure	Anticonvulsants
Thyroid disorder	Hyperparathyroid treatment- Vitamin D analogs Hypothyroid agent

3.3.2 Process to Identify PCL and Control Pharmacies

PCL was implemented between 2016 and 2018 in 15 health system pharmacy sites (UW Health) and 48 community pharmacy sites of 5 organizations (Hayat, Hometown, Forward and Fitchburg Family pharmacy) in Wisconsin. All UW Health pharmacy sites implemented PCL on the same date while each community pharmacy site started using PCL on a different date. Pharmacy characteristics, including the pharmacy types, where the pharmacy was located, and the prescription quantity, may be associated with the decision- making process on the pharmacy side of whether or not the pharmacy decided to participate the PCL intervention. In addition, these characteristics may also relate to the quality of pharmaceutical services provided by the pharmacy and could affect patient's medication use and their medication adherence. Thus, the below process was followed for identifying the PCL participating pharmacies and the control pharmacies that shared similar characteristics as the PCL pharmacies.

A list of the PCL participating pharmacies was obtained from WHL. To identify the PCL pharmacies, we linked this dataset to the Medicaid data to identify the 63 participating pharmacy locations. For control pharmacy identification, we first limited pharmacies that did not implement the PCL during the study period located in the same counties of the 63 PCL pharmacies. We obtained pharmacy-level characteristics of the 63 PCL pharmacies and 617 pharmacies including the provider name, county and ZIP codes of where the pharmacy was located from the National Plan and Provider Enumeration System (NPPES) National Provider Identifier (NPI) Registry. [84]

The RUCA Codes for each pharmacy were generated based on the 2010 Rural-Urban Commuting Area Codes ZIP codes file. [85] The prescription quantity for each pharmacy during the study period was measured by the number of 30-day adjusted fills and was computed using the Medicaid pharmacy claims data. We categorized these pharmacies into a health system pharmacy, or a community pharmacy based on the provider name and author's knowledge. A health system pharmacy was defined as a pharmacy site that belongs to a clinic, hospital, or health care organization that provides medical care in addition to pharmaceutical care.

Community pharmacy includes chain and independent pharmacy organizations. Long-term care specialty pharmacy, and compounding pharmacies were excluded.

We adopted several steps to include control pharmacy with similar characteristics as the treatment pharmacies and to assign the same PCL start date of the treatment pharmacy to its corresponding control pharmacies:

1. Control health system pharmacies (control for UW Health PCL pharmacies): All pharmacies belonging to SSM Health, Aurora and Froedtert Health located in the metropolitan area of the three largest counties in Wisconsin (Dane, Milwaukee, and Waukesha) were identified as control pharmacies for 15 UW Health PCL pharmacies (all located in the metropolitan area of Dane County). The same intervention start date as all the PCL UW Health pharmacies was assigned to these control pharmacies.
2. Control community pharmacies (control for 48 Hayat, Hometown, Forward, and Fitchburg Family PCL pharmacies): For each PCL community pharmacies, two community pharmacies that did not implement the PCL with the same RUCA codes area were selected as control.
    - Metropolitan area: Control pharmacies were first identified from community pharmacies located in the same ZIP code area of the same county that had the closest prescription quantity during the study period. If such a control pharmacy was not available, a control pharmacy was chosen from a neighboring ZIP code area, or from a ZIP code area with the same RUCA codes of a nearby county.
    - Non-metropolitan area: Control pharmacies were selected from community pharmacies located in the same county that had the closest prescription quantity. If such a pharmacy is not available within the county, control pharmacies in the

neighboring county with the same RUCA category and closest prescription quantity were used as control.

Table 3.2 shows pharmacy characteristics for the PCL pharmacies and control pharmacies in Wisconsin are reported by pharmacy type.

Table 3.2 Characteristics of control and treatment pharmacies

	PCL (treatment) pharmacy		Control pharmacy		P-value
	n	%	n	%	
Health system pharmacy	15	100.0	28	100.0	
RUCA codes					
Metropolitan	15	15	28	100.0	.
Prescription quantity(30day-adjusted)					
≤10,000	4	26.7	11	39.3	
>10,000-25,000	5	33.3	6	21.4	
>25,000-50,000	0	0.0	7	25.0	0.057
>50,000	6	40.0	4	14.3	
Community pharmacy	48	100.0	96	100.0	
RUCA codes					
Metropolitan	34	70.8	68	70.8	
Micropolitan	7	14.6	14	14.6	1.000
Small Town	6	12.5	12	12.5	
Rural	1	2.1	2	2.1	
Prescription quantity(30day-adjusted)					
≤10,000	14	29.2	14	14.6	
>10,000-25,000	19	39.6	35	36.5	0.079
>25,000-50,000	9	18.8	21	21.9	
>50,000	6	12.5	26	27.1	

Abbreviations, RUCA: Rural Urban Commuting Area

3.3.3 Inclusion and Exclusion Criteria

Figure 3.2 summarizes each step of the sample identification process. To be included in the study cohort, Medicaid enrollees had to meet the following inclusion criteria: (1) were age ≥ 18 as of January 1st, 2015, (2) were continuously enrolled in Medicaid for each month during the study period (January 2015 to December 2019), (3) were not dual eligible, (4) were not hospitalized for ≥ 90 days at any time during the study period, and (5) received at least one prescription medication fill for a solid oral dosage form to manage one of sixteen chronic conditions (**Table 3.1**) from one of the 63 treatment pharmacy or 124 control pharmacies (**Table 3.2**).

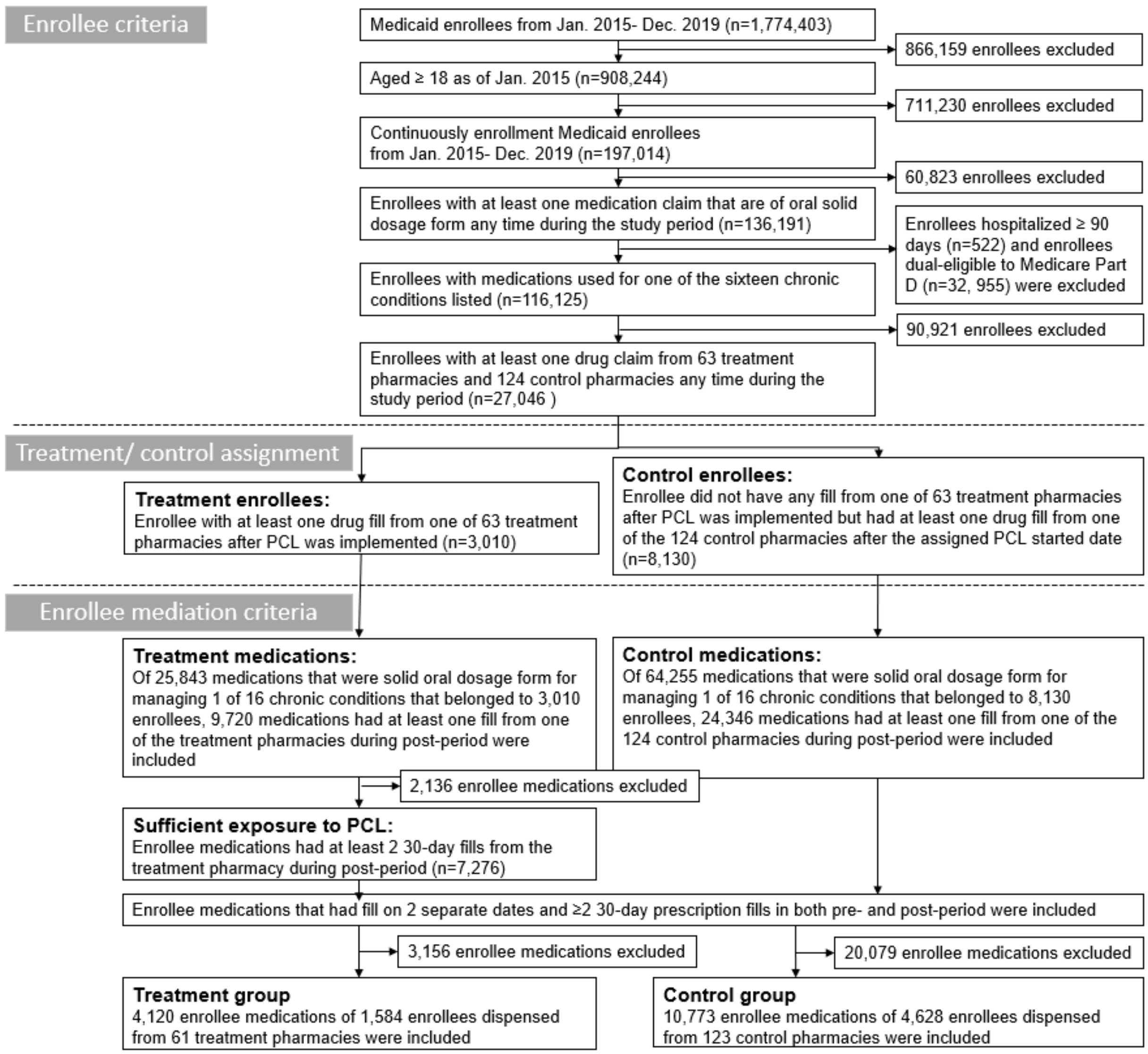


Figure 3.3 Results of sample identification

27,046 Medicaid enrollees who met the inclusion criteria were assigned to either the treatment or control group based on their exposure to PCL, which was determined by whether they received a chronic medication drug fill from the PCL pharmacy after the new label was adopted. Of the 27,046 enrollees, 3,010 enrollees were assigned to the treatment group as they had at least one chronic medication fill from one of the PCL pharmacies during the post-period. Of the remaining 24,036 enrollees who did not receive a chronic medication fill during the post-period from the PCL pharmacies, only 8,130 enrollees had at least one chronic medication fill from one of the control pharmacies and were assigned to the control group.

Of the 25,834 medications that were of solid oral dosage form to manage one of sixteen chronic conditions medications and dispensed to 3,010 enrollees in the PCL group, 9,720 medications were included in the treatment medication sample as they were filled at least once from the treatment pharmacy. To be included in the study sample, medications had to have at least two fills on two unique dates, which summed up to at least two 30-day adjusted supplies from any pharmacies during the pre-period. Additionally, treatment medications had to have at least two fills on two unique dates, with at least two 30-day adjusted supplies from the PCL pharmacies during the post-period. The final treatment cohort contains 4,120 enrollee medications that belonged to 1,585 enrollees dispensed from 61 treatment pharmacies.

8,130 control group enrollees had 64,255 medications that were of solid oral dosage form and were used to manage one of the sixteen chronic conditions. Only 24,346 medications had at least one fill from the control pharmacies during the post-period and were included in the analysis. The control medications had to have at least two fills on two separate dates that summed up to at least two 30-day adjusted supplies during the pre-period from any pharmacies, and at least two fills on two separate dates, with at least two 30-day adjusted supplies during the post-period from one of the control pharmacies. The final control cohort includes 10,773 enrollee medications that belonged to 4,628 enrollees that were filled from 123 control pharmacies.

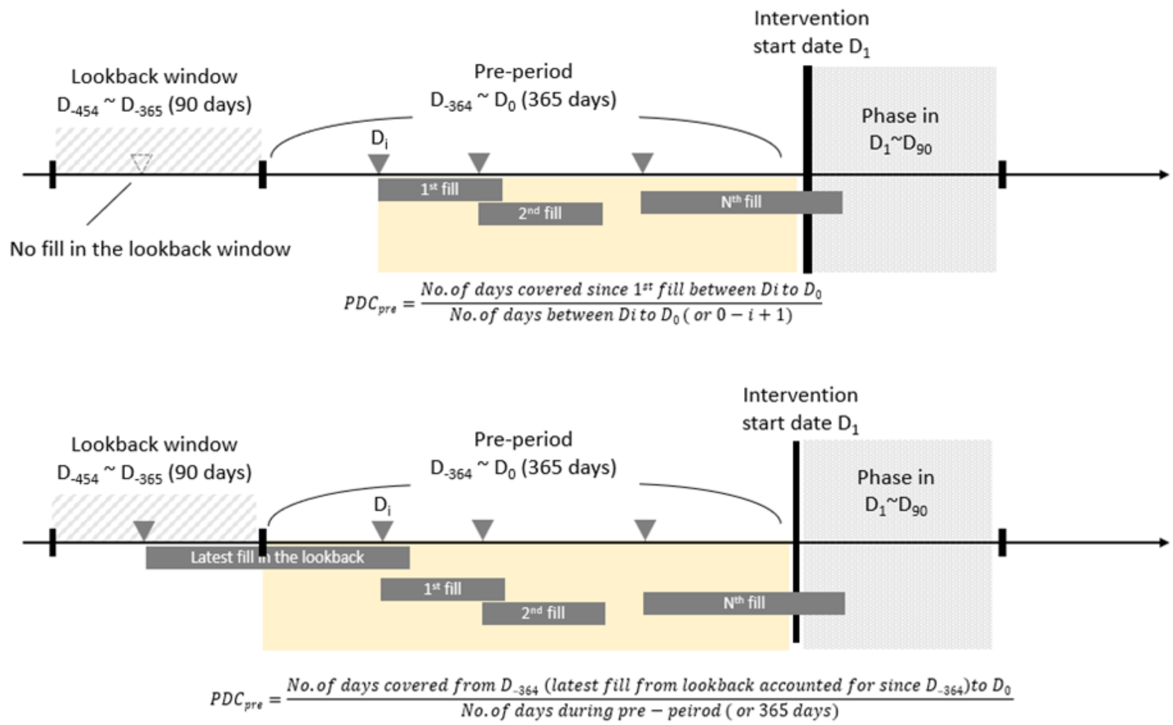
3.4 Medication Adherence Measure – Proportion of days covered (PDC)

Medication adherence was estimated by calculating the proportion of days covered (PDC). PDC is the most commonly used and recommended metric for measuring medication adherence using claims data.[88,89] It is a ratio consisting of the number of days that a person had a particular medication in their possession, based on fill dates and days supply of medication obtained, relative to the total number of days that a person was taking the particular medication. PDC was calculated at the medication level (i.e., same drug ingredient). Medication oversupply was accounted for by shifting the next fill date forward to the day after the days supply of medication from the previous fill was exhausted. As such, the value of PDC for a particular medication cannot exceed 100%. PDC with adjustment for oversupply was calculated in both the pre-period and the post-period. The ***medadhere*** Stata package was used when estimating PDC. [90]

3.4.1 Pre-period PDC Calculation

As shown in **Figure 3.4**, the timeframe used for calculating the pre-period PDC depended on whether patients had days covered by the medication supply during the lookback window, defined as 90 days prior to the beginning of the pre-period. If at least one fill for the medication was identified during the lookback window, the entire length of the pre-period was used in the denominator to estimate the pre-period PDC. The days supply of medication remaining from the last drug fill during the lookback period on the first day of the pre-period was used in calculating the pre-period PDC. If there were no fills of a medication during the lookback window, the length of time a medication was used (i.e., denominator) started on the date of the first medication fill in the pre-period and continued until the end of the pre-period.

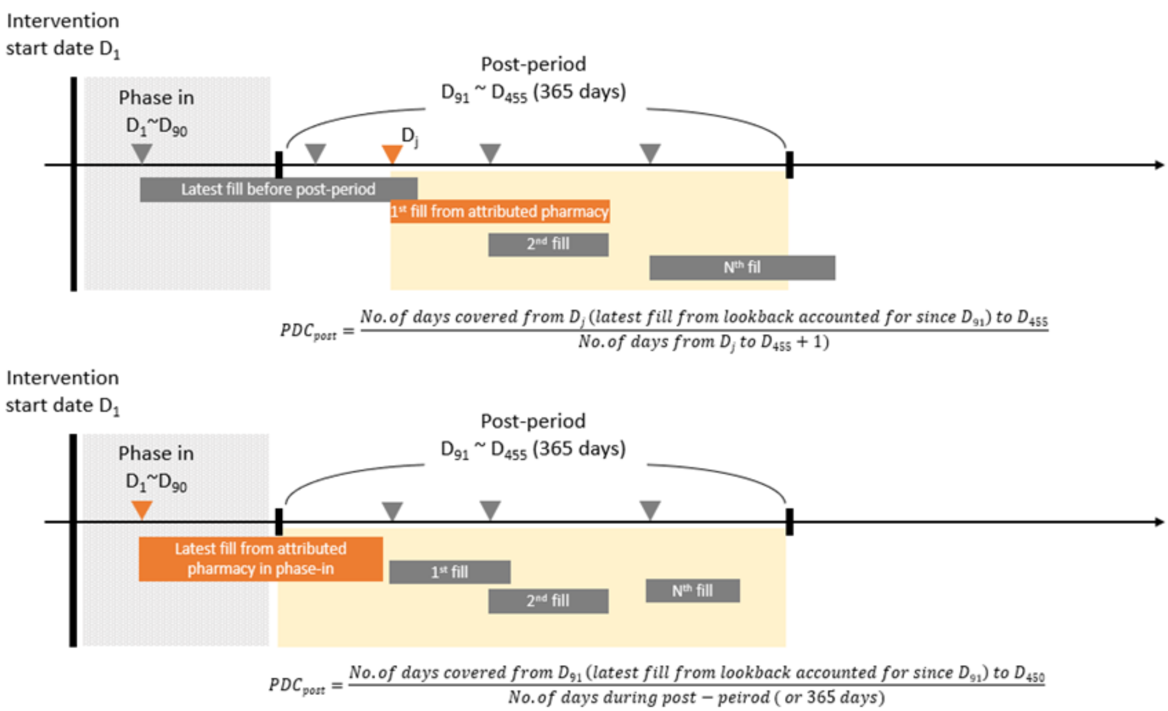
Figure 3.4 Calculation of pre-period PDC



3.4.2 Post-period PDC Calculation

Calculation of post-period PDC is illustrated in **Figure 3.5**. For post-period PDC, only the time period following initial exposure to an attributed pharmacy (i.e., either PCL pharmacy or control pharmacy) was used to calculate PDC. As such, the date when the medication was first filled at an attributed pharmacy was considered the first day of medication supply and the beginning of the time period in which the medication was to be used (i.e., denominator). If at least one drug fill was dispensed from the attributed pharmacy during the phase-in period, the entire post-period was used as the post-period PDC estimation timeframe, and the days supply from the latest fill in the phase-in period to the first date of the post-period was used. Otherwise, the date when the medication was first filled from the attributed pharmacy during the post-period until the last date in the post-period was used as the estimation timeframe for post-period PDC.

Figure 3.5 Calculation of post-period PDC



3.5 Theoretical Framework

Andersen's Behavior Model of Health Services Use was used as a guiding theoretical framework to identify covariates associated with medication use. [91] According to the Anderson Model, the determinants of health services use are often categorized into predisposing, enabling and need characteristics. Predisposing characteristics are individual or environmental factors that affect an individual's predisposition and propensity to use health services; enabling characteristics are defined as the current community and personal resources that allow and facilitate the use of health services; need characteristics represent an individual's actual or perceived health that necessitates the use of health services.

Following the Andersen's model, member characteristics related to age, sex, race and ethnicity were included as predisposing factors. The RUCA codes where the enrollees resided and where the pharmacy was located were used as enabling factors that facilitate medication use. For need factors, Carlson Comorbidity Index and therapeutic categories of medication used were included. Pharmacy type and Medicaid prescription quantity were also included to control for variations in pharmacy characteristics. In addition to the covariates based on the Andersen's model, the study also considers therapy-related factors that could affect medication adherence. [92] Given the data availability, the number of concurrent chronic medications and daily dosing frequency were included as time-varying covariates in the regression model.

CHAPTER FOUR: MANUSCRIPT #1

Title: The Impact of the Wisconsin Patient-centered Prescription Label on Medication Adherence in a Wisconsin Medicaid Population

Target for submission: Am J Health System Pharm, Practice Research Reports

Abstract

Background: Misunderstanding of instructions on prescription drug labels is associated with medication nonadherence, which can lead to poor clinical outcomes and an increase in avoidable healthcare use and cost. Medicaid populations are at disproportionately high risk of medication nonadherence. 63 pharmacy locations in Wisconsin, between late 2016 and 2018, implemented a patient-centered prescription drug labeling (PCL) using the guidelines contained in the United States Pharmacopeia (USP) Chapter 17. The intervention re-designed the label to enhance its clarity and readability However, the effect of Wisconsin PCL intervention on medication adherence was not assessed. Thus, the objective of this study is to evaluate the average treatment effect of PCL on medication adherence among Medicaid enrollees.

Methods: Data from the Wisconsin Medicaid program were obtained. Medications dispensed from pharmacies participating in the PCL label re-design were identified as the treatment group and medications dispensed from pharmacies that did not adopt the PCL label was defined as the control group. The study measured medication adherence by the proportion of days covered (PDC). Ordinary least squares (OLS) difference-in-differences analyses were performed to evaluate the pre-post change in mean PDC between the treatment and control groups after PCL was introduced. Andersen's Behavioral Model was used to guide the inclusion of covariates. Sensitivity analyses with medication adherence defined as PDC≥ 80% with OLS and logistic regression difference-in-differences regression models were also conducted.

Results: The PCL improved mean PDC by 1.17 percentage points in the treatment group relative to the control group following the label change. Sensitivity analyses found consistent results.

Conclusion: PCL may serve as an effective strategy to improve adherence to chronic medications taken by Medicaid enrollees. Future studies should examine the heterogenous effect of PCL on Medicaid enrollees with varying characteristics.

4.1 Introduction

Almost half of the patients are unable to correctly interpret prescription dosage instructions located on prescription labels,[7] which can lead to medication nonadherence, resulting in suboptimal treatment outcomes, and increased hospitalizations, health care costs, medication errors or adverse drug events.[1–6] This is especially common for patients with limited health literacy[7,8] that is often associated with disadvantaged socioeconomic status, being in a racial or ethnic minority group, or having complex oral medication regimens.[7–9]

One potential strategy to improve patient understanding of prescription drug labels and medication adherence is improving the clarity and readability of information contained on prescription drug labeling. In 2013, the United States Pharmacopeia (USP) renewed a set of standards for prescription drug labeling, which emphasize on use of proper format, organization of information and simple language, to promote patient understanding of prescription drug labels and safer medication use. Prescription drug labels that followed these standards are often referred as patient-centered prescription drug labels (PCL).

Starting in 2014, Wisconsin Health Literacy (WHL) initiated a research project to facilitate the adoption of the USP standards and implement prescription label changes in pharmacies in Wisconsin. [10] Between 2016-2018, prescription drug label changes following USP standards were successfully implemented in 5 pharmacy organizations representing 63 pharmacy locations in Wisconsin. Each pharmacy organization changed its labels using different combinations of the USP standards and parameters provided by its pharmacy software vendor.

The preliminary evaluation of the Wisconsin PCL program based on one studied pharmacy organization showed improvement in medication adherence measured by medication possession ratio (MPR) before and after the label change. [11,12] However, the finding is based on only 288 patients without a comparison group. Such single group design may be susceptible to threats to internal validity due to sequential trends. Additionally, although some studies investigating the effectiveness of PCL that incorporates the Universal Medication Schedule (UMS) or USP standards showed that the PCL approach improved patients' understanding of medication instructions,[9,13–16] the findings about its impact on medication adherence are inconclusive.[17–22] The overall effect of PCL in Wisconsin remains unclear. Research to evaluate the effects of the PCL by expanding the sample size of patients impacted by the PCL and improving the study design by including a control group of patients not exposed to the PCL is needed. The objective of this study is to examine the effect of PCL implemented in Wisconsin on medication adherence.

4.2 Methods

Study Design

The study used a pre-test-post-test, non-equivalent control group design with a difference-in-difference approach, to test for changes in medication adherence following the prescription label change in 64 Wisconsin pharmacies. The pre-period was defined as 365 days before the changed prescription label was first used in each pharmacy in the treatment group. The post-period was defined as the 365 days following a 90-day phase-in period after the initial use of the changed label. Medication adherence during the 90-day phase-in period was not estimated to avoid variation that might occur when a new prescription label was introduced at an early stage in participating pharmacies.

Inclusion Criteria

The new PCL label was adopted by 64 Wisconsin pharmacy sites from late 2016 to 2018, which were defined as treatment pharmacies in this study. The study also included pharmacies that did not adopt the PCL label and had similar characteristics as the treatment pharmacy as the control group pharmacies. For 15 UW Health PCL pharmacies (all located in the metropolitan area of Dane County) in the treatment group pharmacies, the corresponding control pharmacies were all pharmacies affiliated with one of the three health systems, SSM Health, Aurora and Froedtert Health, that were located in the metropolitan area of the three largest counties in Wisconsin (Dane, Milwaukee, and Waukesha). For each of the community pharmacies within the treatment group, two control pharmacies were selected based on pharmacy location (RUCA codes, county, and Zip codes), as well as the Medicaid 30-day adjusted prescription quantity during the study period that is closest to the corresponding treatment group pharmacies. The same PCL start dates as their corresponding PCL pharmacies were assigned to the control pharmacies.

Medicaid enrollees to include in the study cohort had to meet the following inclusion criteria: (1) were age $\geq$ 18 as of January 1st, 2015, (2) were continuously enrolled in Medicaid for each month during the study period (January 2015 to December 2019), (3) were not dual eligible, (4) were not hospitalized for $\geq$ 90 days at any time during the study period, and (5) received at least one prescription medication fill for a solid oral dosage form to manage one of sixteen chronic conditions (**Appendix B1**) from one of the 63 treatment pharmacy or 124 control pharmacies.

Medicaid enrollees who met the inclusion criteria were assigned to either the treatment or control group based on their exposure to PCL. An enrollee was assigned to the treatment group if they had at least one prescription for a solid oral dosage form to manage a chronic condition filled at a PCL pharmacy during the post-period. An enrollee that had prescriptions for a solid oral dosage form to manage a chronic condition filled from a control pharmacy, but never filled at a PCL pharmacy during the post-period, was assigned to the control group.

Solid oral dosage form chronic medications dispensed to each enrollee in the treatment group were included in the treatment medications if they (1) were filled at least once during the post-period from one of the treatment pharmacies; (2) had at least two fills on two unique dates, which summed up to at least two 30-day adjusted supply during the pre-period from any pharmacy; and (3) had at least two fills on two unique dates, which summed up to at least two 30-day adjusted supplies during the post-period, with at least two 30-day adjusted supplies from the treatment pharmacy. Chronic medications that are oral solid dosage form dispensed to each enrollee in the control group were included in the control group sample if the following criteria were met: (1) were filled at least once during post-period from one of the 124 control pharmacies and were never filled from any treatment pharmacies after the PCL implementation; (2) had at least two fills on two separate dates that summed up to at least two 30-day adjusted supplies during the pre-period from any pharmacy; and (3) had at least two fills on two separate dates that summed up to at least two 30-day adjusted supplies during the post-period from any pharmacy. Each enrollee medication was attributed to the specific treatment or control pharmacy that dispensed most of their prescription fills during the post-period.

Data Source

The study used Wisconsin Medicaid data files in combination with other data sources to construct an analytical data file. Medicaid data files included a Medicaid member characteristics file, an enrollment file, a hospitalization file, medical encounter files (outpatient visit, ER visit and HMO visit) and a pharmacy claims file for Medicaid fee-for-service enrollees from January 2015 to December 2019. Other data sources included a listing of the pharmacy name and addresses for pharmacies in the PCL group obtained from WHL, and a listing of all licensed pharmacies in Wisconsin obtained from the Department of Safety and Provider Services. The pharmacy-level National Provider Number (NPI) was linked to each pharmacy in the PCL group using information obtained from the Centers for Medicare and Medicaid Services (CMS) National Plan and Provider Enumeration System (NPPES) NPI Registry website.[84] The 2010 Rural-Urban Commuting Area (RUCA) ZIP code file [85] from the US Department of Agriculture Economic Research Service was also used to assign a RUCA code corresponding to the zip code of each pharmacy's location and Medicaid enrollee's residential location.

Outcome Variable

The outcome variable is medication adherence measured by the proportion of days covered (PDC). PDC is the most commonly used and recommended metric for measuring medication adherence using claims data.[88,89] PDC is a ratio consisting of the number of days that a person had a particular medication in their possession, based on fill dates and days supply of medication obtained, relative to the total number of days that a person was taking the particular medication. PDC was calculated at the medication level (i.e., same drug ingredient). Medication oversupply was accounted for by shifting the next fill date forward to the day after the days supply of medication from the previous fill was exhausted. As such, the value of PDC for a particular medication cannot exceed 100%. PDC with adjustment for oversupply was calculated in both the pre-period and the post-period.

The timeframe used for calculating the pre-period PDC depended on whether patients had days covered by the medication supply during the lookback window, defined as 90 days prior to the beginning of the pre-period. If at least one fill for the medication was identified during the lookback window, the entire length of the pre-period was used in the denominator to estimate the pre-period PDC. The days supply of medication remaining from the last drug fill during the lookback period on the first day of the pre-period was used in calculating the pre-period PDC. If there were no fills of a medication during the lookback window, the length of time a medication was used (i.e., denominator) started on the date of the first medication fill in the pre-period and continued until the end of the pre-period.

In calculating the post-period PDC, only the time period following initial exposure to an attributed pharmacy (i.e., either PCL pharmacy or control pharmacy) was used to calculate PDC. As such, the date when the medication was first filled at an attributed pharmacy was considered the first day of medication supply and the beginning of the time period in which the medication was to be used (i.e., denominator). If at least one drug fill was dispensed from the attributed pharmacy during the phase-in period, the entire post-period was used as the post-period PDC estimation timeframe, and the days supply from the latest fill in the phase-in period to the first date of the post-period was used. Otherwise, the date when the medication was first filled from the attributed pharmacy during the post-period until the last date in the post-period was used as the estimation timeframe for post-period PDC.

Statistical Analysis

Descriptive statistics were calculated to summarize the pre-period characteristics between the PCL treatment and control group at the pharmacy, enrollee and medication level. Chi-squared tests were used to test for association between the PCL and control groups in the study variables. T-tests were used to examine pre-post differences in the mean PDC within and between the treatment and control groups.

Multivariate difference-in-difference models using ordinary least squares (OLS) regression were adopted using the full sample of patient medications to estimate the pre-post change in PDC between the treatment group and control group, controlling for demographic, socioeconomic, pharmacy, and health status variables that could be associated with PDC. The inclusion of covariates was based on the Andersen Behavioral Model of Health Services Utilization. Age, sex and race and ethnicity were included as predisposing factors for medication use. The RUCA codes corresponding to where Medicaid enrollees resided and where dispensing pharmacies were located represented enabling factors. The therapeutic category of medications and the Carlson Comorbidity Index, computed based on ICD-10 diagnosis codes,[93] were adjusted for as need variables. Pharmacy type and Medicaid prescription quantity were also controlled for at the baseline. The number of concurrent chronic medications and daily dosing frequency were included as time-varying therapy-related factors that could affect medication adherence 28 in the regression model.

All statistical analyses were conducted using Stata/MP 17 (StataCorp, College Station, Texas). Standard errors were clustered at the person level, and statistical significance was set at an a priori level of <0.05.

Sensitivity Analysis

Sensitivity analyses were conducted to check the robustness of the findings. For the full sample, the sensitivity analyses were conducted using the binary proportion adherent (PDC≥80%) as the outcome measure. Two regression models, including the OLS and logistic regression models, were performed.

Additional sensitivity analyses were performed to further investigate the effect of PCL on medication adherence by exposure level. There was variation in the magnitude with which a patient was exposed to the changed label in the treatment group based on the number of days and how often a medication was filled with the changed label. Therefore, the study stratified the treatment sample by the PCL exposure level, a proportion calculated as the total days supply of medication obtained only from the assigned PCL pharmacy divided by the total days supply of the medication obtained from all pharmacies during the post-period. Each stratified treatment sample was compared with a control stratified sample with the same proportion, which was calculated as total days supply of medication obtained only from the assigned control pharmacy divided by the total days supply of the medication obtained from all pharmacies during the post-period. Three sets of difference-in-difference analyses were performed within each stratum to estimate the effect of PCL on medication adherence by PCL exposure level: one using the mean PDC as the dependent variable and the multivariate OLS regression model, and another two using the binary proportion adherent (PDC≥80%) as the dependent variable with the multivariate OLS and logistic regression models.

4.3 Results

Description of Study Sample

Figure 4.1 presents the flow chart of how the sample of enrollees was identified from the analytical file and how the sample of medications was identified from the analytical file. The PCL group consisted of 61 pharmacies, 1,548 enrollees and a total of 4,120 enrollee medications dispensed during the pre- and post-period. The control group consisted of 123 pharmacies, 4,628 enrollees and 10,773 enrollee medications that were dispensed during the pre- and post-period.

There were no significant differences in pre-period pharmacy characteristics between treatment and control pharmacies (**Table 4.1**). Enrollees in the treatment group were significantly older, had a higher CCI and were using a higher number of concurrent medications relative to enrollees in the control group. A higher proportion of non-Hispanic Black enrollees and a lower proportion of Hispanic enrollees were in the treatment group. No significant difference was found in the distribution of gender and residential area (**Table 4.2**). For enrollee medication characteristics, a significant difference in the distribution of therapeutic categories was found between treatment and control groups (**Table 4.3**).

Effects of PCL on Medication Adherence

Table 4.4 shows the results of the difference-in-difference analyses. For the primary analysis, the mean PDC significantly increased from 84.10% to 85.55% in the treatment group, while it remained stable at approximately 85% in both periods for the control group. A fully adjusted difference-in-difference OLS regression showed that the mean PDC significantly increased by 1.17 percentage points ($p= 0.038$) in the treatment group post PCL implementation relative to the control group. Sensitivity analyses suggested consistent results (**Table 4.4**). The multivariate OLS regression model found that the proportion of medications with PDC$\geq$ 80%

significantly increased by 3.58 percentage points (p=0.002) and the multivariate logistic regression model indicated the odds of being adherent significantly increased by 20% (p = 0.002) in the treatment group following the PCL implementation. Results for full regression models were reported in **Appendix B2**.

Table 4.5 presents the distribution of the PCL exposure level for the treatment group alongside their corresponding control group for each stratification of PCL exposure level. About 84% of the medications in the treatment group were exposed to PCL labels for 100% of the supply days. The treatment group had a significantly higher proportion of medications with the lowest PCL exposure level (<0.50) and the highest exposure level (=1). The average number of days covered by fills dispensed from the attributed pharmacy in these two strata was also higher in the treatment group compared to the control group. Medications in the 0.50-<0.75 stratum and 0.75-<1 stratum were combined due to the smaller sample size. The differences-in-differences analyses by the PCL exposure level found PCL significantly increased medication adherence only in the 100% PCL exposure stratum (adjusted difference-in-difference 1.21 percentage points, p=0.046 for OLS regression model using mean PDC as the outcome measure; adjusted difference-in-difference 3.74 percentage points, p=0.046 for OLS regression model using proportion adherent (PDC≥80%) as the outcome measure; adjusted odds ratio 1.22, p=0.003 for logistic regression model using proportion adherent (PDC≥80%) as the outcome measure). Full results of the difference-in-difference regression models are presented in **Appendix B3-B5**.

4.4 Discussion

The study examined the changes in medication adherence in adult Wisconsin Medicaid enrollees who received a drug fill with the PCL label implemented in certain Wisconsin pharmacies. With a difference-in-difference approach, a slight but significant improvement in medication adherence was found among chronic medications with a PCL label exposure relative to medications that did not. Previous studies found mixed results in medication adherence with interventions to improve prescription label contents[17–22], and only four studies used a comparison group to prevent changes due to history effects.[17,18,21,22] The findings from this study add more evidence on how the PCL label can affect medication adherence among a Wisconsin Medicaid population.

Overall, the magnitude of change in medication adherence from this study is consistent with previous research with positive findings, such that the effect of PCL on medication adherence is relatively minor.[17,22] However, a 1.17 percentage points improvement in medication adherence can total up to 4 more supply days during a fixed one-year period in the treatment group relative to the control group. The clinical relevance of such improvement is unclear and, if any, is likely to be relatively minor. Patients' medication-taking behavior is particularly complex and can be influenced by multiple factors.[92] Thus, muti-faucet strategies to enhance medication adherence is more preferred than intervention with single components.[94] This PCL label can be considered as one approach that can be used in combination with other interventions to optimize medication adherence.

Future Research

Other studies found that the effects of PCL on medication adherence may vary by different patient characteristics, such as medication adherence at baseline, the number of concurrent medications, the daily dosing frequency, as well as the patient's health literacy, education, and self-efficacy level. [18,21,22] According to findings from previous studies, patients with a greater risk profile to nonadherence, including those who had limited health literacy, those who were taking multiple medications and had higher daily dosing frequency, tend to benefit more from the PCL label with improved medication adherence. [18,21,22] Additionally, it is also likely that the PCL intervention may have a different effect on medication adherence across varied disease categories, and different complexity levels of medication regimens. Notably, in this study, coefficients of health system pharmacy type indicated that medication adherence was significantly lower among medications dispensed from a health system pharmacy relative to a community pharmacy. This may be due to the widespread adoption of automatic prescription refill programs in community pharmacies.[95,96] Other coefficients of certain covariates also suggested medication adherence was significantly lower among medications being taken by someone with older age, medication being taken by non-Hispanic Black, Hispanics and others as compared to non-Hispanic White, medications with higher daily dosing frequency, as well as medication used for managing certain therapeutic categories (**Appendix B2**). Further investigation on the heterogeneous effect of the PCL label is needed, especially among those with characteristics that are associated with lower medication adherence, for a better understanding of the intervention and to inform providers about the label design.

Limitation

The study has several limitations that need to be noted. First, the study measured medication adherence by PDC. The measurement assumes prescription refilling behavior corresponded to patients' actual medication taking behavior. [97] Thus, it tends to overestimate medication adherence. However, when only prescription claims data or refill records are available, PDC is the measure with a relative lower risk of overestimation relative to MPR.[98] Further, as this study used a pre-test-post-test, non-equivalent control group study design, the same overestimation should occur in both control and treatment groups during pre-and post-periods; threat to internal validity due to such limitation is not likely.

Secondly, there are some uncertainties in the exposure. The actual components changed on the new label for each pharmacy were not known and variations on the new labels may exist across pharmacy sites. It is unknown how the changed prescription drug labels impacted patient adherence. Further data collection and examination of each component may be conducted to better understand the effect of PCL. Additionally, the extent and pattern to which each patient in the treatment group was exposed to the PCL label for each of their chronic medications cannot be observed. The information on whether the enrollee read the new label each time when the medication was dispensed from the pharmacy or when they were taking the medication was not available. It is also likely that an enrollee may utilize pill organizers to arrange their medications and discard the label afterward. However, the study made the first attempt to categorize PCL label exposure. From the sensitivity analysis results, only improvement in mediation adherence was found for the stratum with 100% PCL exposure, a stratum consisting of medications that were dispensed 100% from their attributed intervention or control pharmacy. The results suggested that PCL is effective to increase medication adherence when the treatment medications were constantly attached with a PCL label dispensed from the same treatment pharmacy across the study period, compared to control medications that were refilled consistently at the same control pharmacy. No significant change in medication adherence was found for medications with lower PCL exposure. This could indicate PCL labels may have a relatively short-term effect on medication adherence, such that once the patients switched to pharmacies that did not dispense medication with a PCL label, their medication adherence dropped. However, the finding should be interpreted with caution, as the sample size for the low PCL exposure might have been too small to detect significant changes in medication adherence.

Third, this study only accounted for the number of concurrent medications and daily dosing frequency as time-varying covariates. There may be other confounders unrelated to the number of concurrent medications and daily dosing frequency that can vary over time and were not controlled for at the baseline in this study. For example, if the disease severity changes over time and affects medication adherence, there could be omitted variable bias. However, no differential effects are expected between the treatment and control groups as a result of this bias.

Lastly, the study may have limited generalizability. Part of the reason is that PCL interventions were only implemented in pharmacies within certain counties in Wisconsin, and most of them are located in metropolitan areas. Whether the effect of the intervention would be the same when it was scaled up to the entire state, including other pharmacies located in rural areas, is not clear. Another reason is due to the inclusion criteria we adopted for sample identification. According to the specifications, only enrollees who were continuously enrolled in Medicaid, and medications with at least two fills on two unique dates, with at least two 30-day adjusted fills during pre-period and post-period were included. Such an approach could have biased the sample towards a relatively stable and adherent population, and the findings may not apply to all Medicaid enrollees who had coverage gaps because of financial difficulties, or to those who have recently begun taking a chronic medication.

4.5 Conclusion

In conclusion, the current study found a small but significant increase in medication adherence among adult Medicaid enrollees who used chronic condition medications and received

PCL labels for the medications. When we stratified the exposure to PCL by the proportion of medication supply days covered through the treatment pharmacy, the only significant effect was seen among enrollees who had 100% of medication supply days covered from the treatment pharmacy. For optimized improvement, the pharmacist can use a patient-centered prescription label in combination with other strategies to enhance patient medication adherence.

4.6 Figures and Tables

Figure 4.1 Study sample

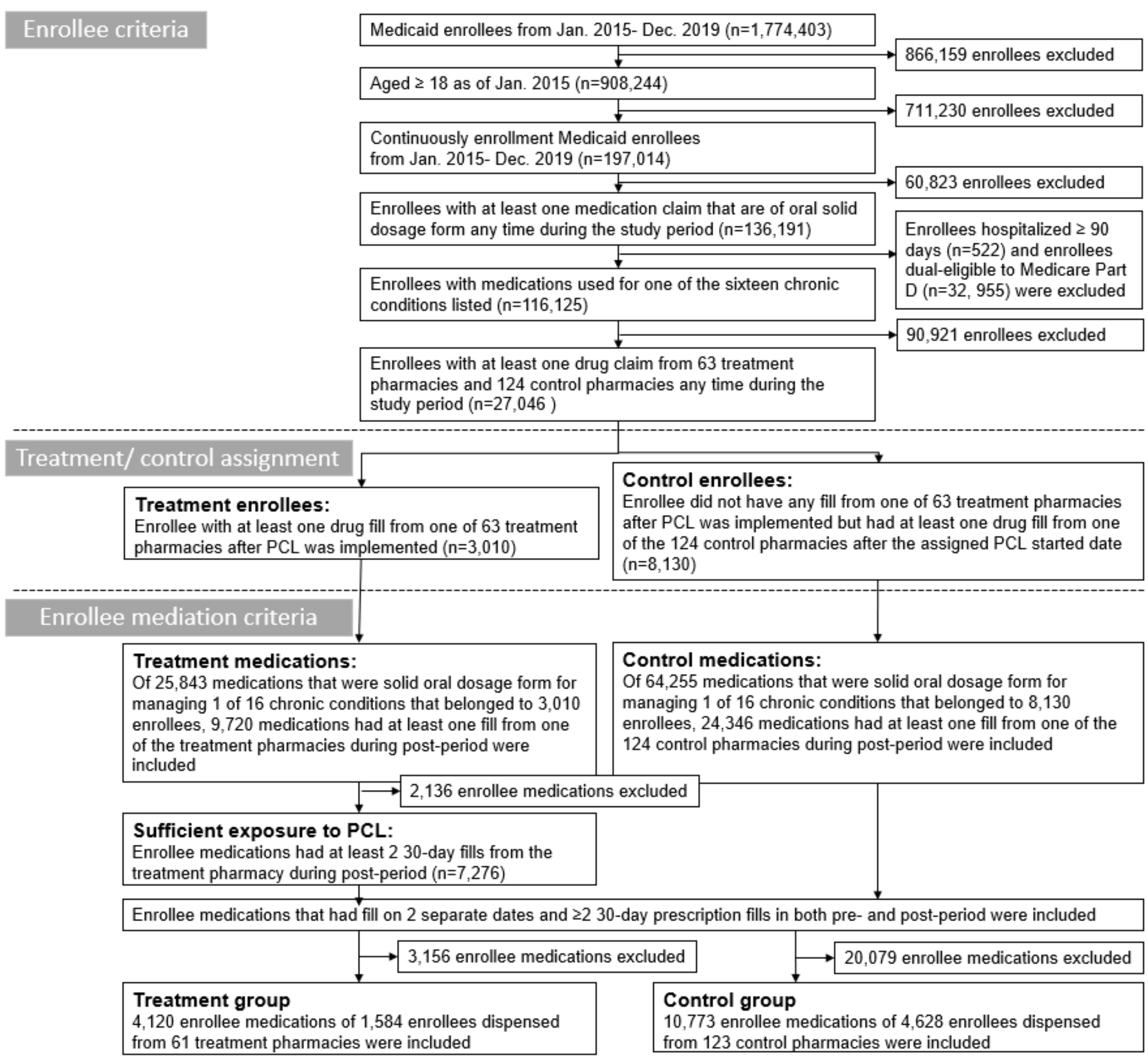


Table 4.1 Pre-period characteristics between treatment and control pharmacies

	Pharmacy				P-value
	Treatment pharmacy (n=61)		**Control pharmacy (n=123)**		
	n	%	n	%	
Health system pharmacy	13	100.0	27	100.0	
RUCA codes					
Metropolitan	13	100.0	27	100.0	.
Prescription quantity(30day-adjusted)					
≤10,000	0	25.9	7	0.0	0.094
>10,000-25,000	4	11.1	3	30.8	
>25,000-50,000	4	40.7	11	30.8	
>50,000	5	22.2	6	38.5	
Community pharmacy	48	100.0	96	100.0	
RUCA codes					
Metropolitan	34	70.8	68	70.8	1.000
Micropolitan	7	14.6	14	14.6	
Small Town	6	12.5	12	12.5	
Rural	1	2.1	2	2.1	
Prescription quantity(30day-adjusted)					
≤10,000	6	27.1	26	12.5	0.107
>10,000-25,000	13	14.6	14	27.1	
>25,000-50,000	20	36.5	35	41.7	
>50,000	9	21.9	21	18.8	

Abbreviations, RUCA: Rural Urban Commuting Area

Table 4.2 Pre-period characteristics between treatment and control enrollees

	Enrollee				P-value
	Treatment (n=1,584)		Control (n=4,628)		
	n	%	n	%	
Age					
18-34	429	27.1	1,526	33.0	0.000
35-44	464	29.3	1,280	27.7	
45-54	504	31.8	1,309	28.3	
55-64	182	11.5	507	11.0	
65+	5	0.3	6	0.1	
Gender					
Female	1,031	65.1	3,114	67.3	0.109
Male	553	34.9	1,514	32.7	
Race					
White, non-Hispanic	936	59.1	2,935	63.4	0.000
Black, non-Hispanic	470	29.7	1,066	23.0	
Hispanic	59	3.7	319	6.9	
Other	119	7.5	308	6.7	
RUCA codes					
Metropolitan	1,220	77.0	3,554	76.8	0.648
Micropolitan	164	10.4	460	9.9	
Small Town	139	8.8	402	8.7	
Rural	61	3.9	212	4.6	
Charlson Comorbidity Index					
0	934	59.0	2,834	61.2	0.048
1	394	24.9	1,177	25.4	
2	117	7.4	285	6.2	
≥3	139	8.8	332	7.2	
Number of concurrent medications					
≤3	560	35.4	1,927	41.6	0.000
≥4-6	568	35.9	1,682	36.3	
≥7	456	28.8	1,019	22.0	

Abbreviations, RUCA: Rural Urban Commuting Area

Table 4.3 Pre-period characteristics between treatment and control enrollee medications

	Enrollee Medication				P-value
	Treatment(n=4,120)		Control (n=10,773)		
	n	n	n	%	
Daily dosing frequency (times/day)					
Less than 1	190	4.6	474	4.6	0.376
≥1	2,676	65.0	6,923	65.0	
≥2	831	20.2	2,165	20.2	
≥3	423	10.3	1,211	10.3	
Therapeutic category					
ADHD	221	5.4	792	5.4	0.000
Autoimmune diseases	50	1.2	137	1.2	
Cardiovascular conditions	42	1.0	108	1.0	
Dementia	3	0.1	5	0.1	
Depression	793	19.2	2,082	19.2	
Diabetes	265	6.4	666	6.4	
Diuresis	168	4.1	396	4.1	
Gout	40	1.0	86	1.0	
Hyperlipidemia	323	7.8	799	7.8	
Hypertension	793	19.2	1,866	19.2	
Osteoporosis	113	2.7	229	2.7	
Other mental health	175	4.2	485	4.2	
Parkinson's disease	28	0.7	70	0.7	
Peptic ulcer	383	9.3	940	9.3	
Seizure	584	14.2	1,668	14.2	
Thyroid disorder	139	3.4	444	3.4	

Abbreviations, RUCA: Rural Urban Commuting Area

Table 4.4 Difference-in-difference regression estimates of the effect of PCL on medication adherence

	Treatment Total n=4,120			Control Total n=10,773			Adjusted diff-in-diff.[a]	Adjusted odds ratios [b]
	Pre-period	Post-period	Diff.	Pre-period	Post-period	Diff.		
Primary analysis								
Mean PDC	84.10%	85.55%	1.45***	84.51%	84.79%	0.28	1.17**	
Sensitivity analysis								
Proportion adherent (PDC≥80%)	71.51%	84.37%	2.86**	82.02%	71.31%	-0.72	3.58**	1.20**

[a] Ordinary Least Square regression model adjusted for pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, number of medications per enrollee, the therapeutic category of the medication and the number of times taking the mediation per day.

[b] Logistic regression model adjusted for pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, number of medications per enrollee, the therapeutic category of the medication and the number of times taking the mediation per day.

*Significant at p<0.05, ** significant at p<0.01, ***significant at p<0.001

Table 4.5 Distribution of PCL exposure level of the treatment group and the corresponding control group

	Treatment medications		Control medications		t-test P-value
Proportion of days covered by fills dispensed from the attributed pharmacy, n (%) [a]					
<0.50	229	(5.6)	1,172	(10.9)	0.000
0.50-<0.75	217	(5.3)	589	(5.5)	0.629
0.75-<1	219	(5.3)	564	(5.2)	0.844
1	3,455	(83.9)	8,448	(78.4)	0.000
Average number of days covered by fills dispensed from the attributed pharmacy, mean (range)					
<0.50	87.89	(60-180)	57.92	(1-180)	0.000
0.50-<0.75	137.12	(60-270)	124.39	(28-270)	0.013
0.75-<1	229.65	(60-360)	217.84	(27-365)	0.078
1	237.81	(60-365)	248.57	(3-365)	0.000

[a] Calculated as the number of days covered by the medication supply from drugs fills dispensed from the treatment pharmacy (for treatment medications) or the attributed control pharmacy (for control medications) for each medication during post-period divided by the total number of days covered with medication supply from all drug fills during post-period.

Table 4.6 Sensitivity analyses: Difference-in-difference linear regression estimates of the effect of PCL on medication adherence

	Treatment Total n=4,120 By proportion of days covered: <0.50, n=229 0.5-1, n=436 1, n=3,455			Control Total n=10,773 By proportion of days covered: <0.50, n=1,172 0.5-1, n=1,153 1, n=8,488			Adjusted diff-in-diff. [a]	Adjusted odds ratios [b]
	Pre-period	**Post-period**	**Diff.**	**Pre-period**	**Post-period**	**Diff.**		
Mean PDC								
By proportion of days covered from the attributed pharmacy								
<0.50	85.60%	91.73%	6.13***	81.40%	84.94%	3.54***	2.59	-
0.50-<1	81.07%	83.45%	2.38	81.01%	81.00%	-0.01	2.39	-
1	85.21%	85.41%	0.20	85.42%	84.41%	-1.00***	1.21**	-
Proportion adherent (PDC≥80%)								
By proportion of days covered from the attributed pharmacy								
<0.50	72.05%	82.97%	10.92***	66.38%	71.33%	4.95**	5.97	1.51
0.50-<1	64.91%	68.12%	3.21	66.17%	65.13%	-1.04	4.25	1.22
1	72.30%	74.59%	2.29*	73.60%	72.15%	-1.46*	3.74**	1.22**

[a] Ordinary Least Square regression model adjusted for pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, number of medications per enrollee, the therapeutic category of the medication and the number of times taking the mediation per day.
[b] Logistic regression model adjusted for pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, number of medications per enrollee, the therapeutic category of the medication and the number of times taking the mediation per day.
*Significant at p<0.05, ** significant at p<0.01, ***significant at p<0.001

CHAPTER FIVE: MANUSCRIPT #2

Title: Response to Patient-centered Prescription Label Intervention Targeting Medication Adherence for Medicaid Enrollees with Different Baseline Medication Adherence Levels

Target for submission: J Manag Care Spec Pharm

Abstract

Background: Patient-centered prescription drug labeling is one approach to improve patient understanding of prescription drug label and medication adherence by enhancing the clarity and readability of the drug label. To better understand whether PCL may be an effective strategy to improve medication adherence for those with low baseline medication adherence, the objective of this study is to evaluate the effect of PCL on medication adherence for medications taken by Medicaid enrollees stratified by baseline adherence level.

Methods: Using Wisconsin Medicaid pharmacy claims data, the study identified medications dispensed from pharmacies that changed the drug label as the treatment group and medications dispensed from pharmacies that never used the new label as the control group. We further stratified the study sample by baseline medication adherence. Ordinary least squares (OLS) difference-in-differences analyses were performed to evaluate the pre-post change in medication adherence measured by the mean proportion of days covered (PDC) between treatment and control groups post label change within low (defined as the sample with the lowest 25% PDC at baseline) and high (defined as the sample with above the lowest 25% PDC at baseline) baseline medication adherence strata. Sensitivity analyses using pre-post differences in mean medication adherence and proportion adherent (PDC≥ 80%) as the dependent variable were also conducted.

Results: For medications with low adherence at baseline, the PCL significantly improved the mean PDC by 2.19 percentage points for the treatment group relative to the control group. For medications with high baseline adherence, no significant change in mean PDC was found between the study groups. Results from sensitivity analyses were consistent.

Conclusion: The findings suggested PCL may be one effective strategy to improve medication adherence for those with medication adherence challenges at baseline. Future research should explore the effect of interventions incorporating PCL and other strategies on medication adherence.

5.1 Introduction

Poor adherence to chronic medications is prevalent, and results in severe consequences for Medicaid patients. One possible reason for medication nonadherence is patient misunderstanding or confusion about medication instructions, which can result from low health literacy and poor prescription drug container labeling.[7,40] Approximately 30% of Medicaid enrollees have below basic health literacy level [55] and more than half with chronic diseases were not adherent to their medications.[25,99,100] Medicaid enrollees with lower medication adherence were more likely to use more acute care services including having a hospitalization and emergency room visit[100–103], leading to increased health care costs.[100,102]

Strategies to improve the clarity and readability of prescription drug labels may be a potential solution to poor medication adherence among Medicaid enrollees. In 2013, the United States Pharmacopeia (USP) renewed a set of standards for prescription drug labeling to promote patient understanding of prescription drug labels and safer medication use. In Wisconsin, a research team worked with 63 pharmacy locations to modify existing prescription labels using the USP standards to create a new patient-centered prescription drug label (PCL). The new labels were between 2016 and 2018. A previous analysis showed that the PCL is effective in improving medication adherence by 1.17 percentage points among Medicaid enrollees.

Medication adherence interventions may have heterogeneous effects across patients with different characteristics, including their baseline medication adherence levels.[64] Findings from previous studies are mixed. Some studies have found that individuals with lower baseline medication may be more responsive to an intervention or policy designed to improve medication adherence. [26,65,66] Other studies suggest individuals with higher medication adherence at baseline were more likely to show improvement post-intervention.[52,67] Whether the PCL is effective in improving medication adherence among those who have low baseline medication is unclear and requires further research.

The objective of this study is to evaluate the effect of PCL on enrollees with low and high baseline adherence. The study hypothesizes that the effect of PCL intervention may be larger for enrollees with lower baseline medication adherence. To understand whether the effect of PCL intervention differs by enrollee's pre-intervention adherence, the study sample was stratified by the level of the enrollee's medication adherence before the intervention. The change in medication adherence in treatment relative to control after PCL implementation was estimated for each stratum.

5.2 Methods

Study Design

The study used a pre-test-post-test, non-equivalent control group design with a difference-in-difference approach, to test for changes in medication adherence following the prescription label change in 64 Wisconsin pharmacies. The pre-period was defined as 365 days before the changed prescription label was first used in each pharmacy in the treatment group. The post-period was defined as the 365 days following a 90-day phase-in period after the initial use of the changed label. Medication adherence during the 90-day phase-in period was not estimated to avoid variation that might occur when a new prescription label was introduced at an early stage in participating pharmacies.

Data Source

The study used Wisconsin Medicaid data files in combination with other data sources to construct an analytical data file. Medicaid data files included a Medicaid member characteristics file, an enrollment file, a hospitalization file, medical encounter files (outpatient visit, ER visit and HMO visit) and a pharmacy claims file for Medicaid fee-for-service enrollees from January 2015 to December 2019. Other data sources included a listing of the pharmacy name and address for pharmacies in the PCL group obtained from Wisconsin Health Literacy (WHL), and a listing of all licensed pharmacies in Wisconsin obtained from the Department of Safety and Provider Services. The pharmacy-level National Provider Number (NPI) was linked to each pharmacy in the PCL group using information obtained from the Centers for Medicare and Medicaid Services (CMS) National Plan and Provider Enumeration System (NPPES) NPI Registry website[84]. The 2010 Rural-Urban Commuting Area (RUCA) ZIP code file [85] from the US Department of Agriculture Economic Research Service was used to assign a RUCA code corresponding to the zip code of each pharmacy's location and Medicaid enrollee's residential location.

Study Sample

The new PCL label was adopted by 64 Wisconsin pharmacy sites from late 2016 to 2018, which were defined as treatment pharmacies in this study. The study also included pharmacies that did not adopt the PCL label and had similar characteristics as the treatment pharmacy as the control group pharmacies. For 15 UW Health PCL pharmacies (all located in the metropolitan area of Dane County) in the treatment group pharmacies, the corresponding control pharmacies were all pharmacies affiliated with one of the three health systems, SSM Health, Aurora and Froedtert Health, that were located in the metropolitan area of the three largest counties in Wisconsin (Dane, Milwaukee, and Waukesha). For each of the community pharmacies within the treatment group, two control pharmacies were selected based on pharmacy location (RUCA codes, county, and Zip codes), as well as the Medicaid 30-day adjusted prescription quantity during the study period that is closest to the corresponding treatment group pharmacies. The same PCL start dates as their corresponding PCL pharmacies were assigned to the control pharmacies.

Medicaid enrollees to include in the study cohort had to meet the following inclusion criteria: (1) were age ≥ 18 as of January 1st, 2015, (2) were continuously enrolled in Medicaid for each month during the study period (January 2015 to December 2019), (3) were not dual eligible, (4) were not hospitalized for ≥ 90 days at any time during the study period, and (5) received at least one prescription medication fill for a solid oral dosage form to manage one of sixteen chronic conditions (**Appendix C1**) from one of the 63 treatment pharmacy or 124 control pharmacies.

Medicaid enrollees who met the inclusion criteria were assigned to either the treatment or control group based on their exposure to PCL. An enrollee was assigned to the treatment group if they had at least one prescription for a solid oral dosage form to manage a chronic condition filled at a PCL pharmacy during the post-period. An enrollee that had prescriptions for a solid oral dosage form to manage a chronic condition filled from a control pharmacy, but never filled at a PCL pharmacy during the post-period, was assigned to the control group.

Solid oral dosage form chronic medications dispensed to each enrollee in the treatment group were included in the treatment medications if they (1) were filled at least once during the post-period from one of the treatment pharmacies; (2) had at least two fills on two unique dates, which summed up to at least two 30-day adjusted supply during the pre-period from any pharmacy; and (3) had at least two fills on two unique dates, which summed up to at least two 30-day adjusted supplies during the post-period, with at least two 30-day adjusted supplies from the treatment pharmacy. Chronic medications that are oral solid dosage form dispensed to each enrollee in the control group were included in the control group sample if the following criteria were met: (1) were filled at least once during post-period from one of the 124 control pharmacies and were never filled from any treatment pharmacies after the PCL implementation; (2) had at least two fills on two separate dates that summed up to at least two 30-day adjusted supplies during the pre-period from any pharmacy; and (3) had at least two fills on two separate dates that summed up to at least two 30-day adjusted supplies during the post-period from any pharmacy. Each enrollee medication was attributed to the specific treatment or control pharmacy that dispensed most of their prescription fills during the post-period.

Outcome Variable

The outcome variable is medication adherence measured by the proportion of days covered (PDC), which is the most commonly used and recommended metric for measuring medication adherence using claims data.[88,89] PDC is a ratio consisting of the number of days that a person had a particular medication in their possession, based on fill dates and days supply of medication obtained, relative to the total number of days that a person was taking the particular medication. PDC was calculated at the medication level (i.e., same drug ingredient). Medication oversupply was accounted for by shifting the next fill date forward to the day after the days supply of medication from the previous fill was exhausted. As such, the value of PDC for a particular medication cannot exceed 1.0. PDC with adjustment for oversupply was calculated in both the pre-period and the post-period.

The timeframe used for calculating the pre-period PDC depended on whether patients had days covered by the medication supply during the 90-day lookback window, before their first drug fill in the pre-period. If at least one fill for the medication was identified during the lookback window, the entire length of the pre-period was used in the denominator to estimate the pre-period PDC. The days supply of medication remaining from the last drug fill during the lookback period on the first day of the pre-period was used in calculating the pre-period PDC. If there were no medication fills during the lookback window, the length of time a medication was used (i.e., denominator) started on the date of the first medication fill in the pre-period and continued until the end of the pre-period.

In calculating the post-period PDC, only the time period following initial exposure to an attributed pharmacy (i.e., either PCL pharmacy or control pharmacy) was used to calculate PDC. As such, the date when the medication was first filled at an attributed pharmacy was considered the first day of medication supply and the beginning of the time period in which the medication was to be used (i.e., denominator). If at least one drug fill was dispensed from the attributed pharmacy during the phase-in period, the entire post-period was used as the post-period PDC estimation timeframe, and the days supply from the latest fill in the phase-in period to the first date of the post-period was used. Otherwise, the date when the medication was first filled from the attributed pharmacy during the post-period until the last date in the post-period was used as the estimation timeframe for post-period PDC.

Stratification by Pre-period PDC

Enrollee medication in both the treatment and control groups were stratified by the value of the pre-period PDC into low or high baseline medication adherence subgroups. The PDC value corresponding to the 25th percentile of the PDC distribution was chosen as the cut-off point for forming the subgroups.

Statistical Analysis

Descriptive statistics were calculated to summarize the pre-period characteristics between the PCL and control group at the pharmacy, enrollee and medication levels for samples stratified by low or high baseline medication adherence. Chi-squared tests were used to test for association between the PCL and control groups in the study variables. T-tests were used to examine pre-post differences in the mean PDC within and between the PCL and control groups. T-tests were used for testing the significance of pre-post differences in the mean PDC within the group.

Difference-in-differences analyses were conducted to compare the pre-post change in medication adherence between treatment and control within the low or high medication adherence stratum. Ordinary least squares (OLS) regression was used to control for important demographic, socioeconomic, and health status variables that might be associated with medication use. The inclusion of covariates was based on the Andersen Behavioral Model of Health Services Utilization as well as available characteristics of members in the data. Age, sex and race and ethnicity were included as predisposing factors for medication use. The RUCA codes corresponding to where Medicaid enrollees resided and where dispensing pharmacies were located represented enabling factors. The therapeutic category of medications and the Carlson

Comorbidity Index, computed based on ICD-10 diagnosis codes, [93] were adjusted for as need variables. Pharmacy type and pharmacy Medicaid prescription quantity were also controlled for at the baseline. The number of concurrent chronic medications and daily dosing frequency were included as time-varying therapy-related factors that could affect medication adherence [92] in the regression model.

Two sets of sensitivity analyses were conducted to check the robustness of the finding. The first set of sensitivity analyses used the binary proportion adherent (PDC≥80%) measured at the medication level as the dependent variable and the OLS regression model was performed to estimate the impact of PCL. To better control for regression to the mean, the second set of sensitivity analyses modeled the pre-post difference in the mean PDC as the dependent variable, and added the pre-period PDC alongside with other covariates in the explanatory variables of the OLS regression model. [104]

An additional post-hoc analysis was performed for subgroups of low baseline medication adherence to further examine whether the magnitude of the PCL effect varied with different baseline medication adherence level. Difference-in-difference OLS regression models were performed with the cut-off point of 40% PDC.

All statistical analyses were conducted using Stata/MP 17 (StataCorp, College Station, Texas). Standard errors were clustered at the person level, and statistical significance was set at a level with α of <0.05 in all regression models.

5.3 Results

Study Samples

The categorization as high or low medication adherence was based on the distribution of the pre-period PDC by quartiles for the treatment and control groups presented in **Table 5.1**. the lowest 25% group has a mean PDC between 50-55%, while all the other three groups (the lowest 25%-50%, the highest 25% to 50%, and the highest 25%) have a higher mean PDC value above 80%. Thus, the group with the lowest 25% pre-period PDC was defined as the low baseline medication adherence stratum, and all the other three groups were combined and defined as the high baseline medication adherence stratum.

As shown in **Figure 5.1**, the low baseline medication adherence stratum consists of 1,028 enrollee medications in the treatment group and 2,693 enrollee medications in the control group. The high baseline medication adherence stratum includes 846 and 2,313 enrollee medications in the treatment and control groups, respectively. Within the low baseline medication adherence stratum, 21.8% of enrollee medications in the treatment group and 26.9% of enrollee medications in the control group had baseline PDC values equal to or less than 40%.

There were no significant differences between the control and treatment pharmacies in both the low and high medication adherence groups (**Table 5.2**). However, significant differences in the enrollee characteristics, including the distribution of age, race and ethnicity and the number of concurrent chronic medications, were found between enrollees in the treatment and control groups in both the low and high baseline adherence groups (**Table 5.3**). At the enrollee medication level, significant difference was found in the distribution of medication therapeutic categories between the treatment and control group in both the low and high baseline adherence groups (**Table 5.4**).

Effect of PCL on Medication Adherence

The effects of PCL on medication adherence within each of the low and high pre-period medication adherence groups are contained in **Table 5.5.** For the low baseline medication adherence group, the unadjusted mean PDC increased significantly in both treatment (24.22 percentage points) and control (22.02 percentage points) groups after the PCL was introduced. Results from the fully adjusted differences-in-difference analysis showed a significant improvement in the mean PDC of 2.19 percentage points (p=0.047) in the treatment group after the PCL was introduced compared to the control group. For the high baseline medication adherence group, the unadjusted mean PDC for both the treatment and control groups significantly decreased by 7.04 percentage points and 7.88 percentage points, respectively. The adjusted difference-in-difference estimate showed no significant impact of the PCL. The full results of the difference-in-difference models are presented in **Appendix C1**.

Sensitivity analyses confirmed the results of the OLS difference-in-difference models (**Table 5.6**). In the first set of sensitivity analyses, the adjusted difference-in-difference OLS regression results suggested a significant 8.18 percentage points (p=0.000) increase in the proportion of medications with PDC ≥80% in the treatment group following implementation of PCL relative to the control group for the low baseline medication adherence group. The second set of sensitivity analyses, which estimated an OLS regression model with the pre-post change in mean PDC as the dependent variable, showed a significant increase of 3.98 percentage points (p=0.001) in the mean PDC difference for the treatment group compared to the control group in the low baseline medication adherence group. The results for the full regression models estimated for the sensitivity analyses are contained in A**ppendix C2** and **Appendix C3**.

Table 5.7 summarizes the results of the post-hoc analyses within subgroups of the low baseline medication adherence group. Among medications with PDC < 40%, the mean PDC increased significantly by 4.73 percentage points (p=0.045) in the treatment group relative to the control group after the PCL was started. Among medications with a PDC above 40%, the mean PDC increased significantly by 3.00 percentage points (p=0.019) in the treatment group relative to the control group after the PCL was started. The complete results of the post-hoc analyses are included in **Appendix C4**.

5.4 Discussion

This study evaluated the effects of a PCL label change on medication adherence for chronic medications among Wisconsin Medicaid enrollees. The results showed that enrollee medications with low baseline medication adherence had a statistically significant 2.19 percentage points increase in adherence post PCL implementation. The PCL label change did not significantly improve medication adherence for enrollee medications with high baseline medication adherence.

The results of this study add to the scarce body of literature on the importance of stratified analyses to understand the heterogeneous effect of medication adherence interventions by baseline medication adherence. [26,66,67] Medication adherence at baseline has been identified as a predictor for future medication adherence, [52,105] and patients may respond differently, based on baseline medication adherence, to a changed prescription drug label that is designed to be patient-centric and improve patient readability and understanding of medication instructions. Previous research has investigated the heterogeneous effect of PCL on medication adherence for subgroups of individuals based on characteristics that are associated with poor medication adherence, such as limited health literacy level, number of concurrent medications and daily dosing frequencies. [18,21,22] The current study is one of the first studies known to the author to examine the effects of PCL as an effective strategy to improve medication adherence for patients with relatively low medication adherence before the PCL intervention started. The results showed that the PCL had the greatest effect when medication adherence was 40% or lower in the time period before the PCL was started.

Although not examined directly in this study, it is likely that factors associated with lower baseline medication adherence in this study may be related to difficulties understanding the prescription drug labels. It is likely that a high proportion of enrollees with low medication adherence at baseline may have difficulties understanding the prescription drug labels and were not taking medication as instructed. In that regard, PCL interventions that aim to improve the clarity and readability of prescription drug labels appear to be beneficial in improving patient comprehension of prescription drug labels and subsequent medication taking behavior. However, there can be other reasons for low medication adherence at baseline that cannot be addressed by the PCL intervention. In this case, PCL may be incorporated with other attitudinal, educational or technical interventions or as a multifactorial approach that targets the root causes of medication nonadherence to improve medication adherence.[106,107]

No significant change in medication adherence for enrollee medications with relatively high medication adherence at baseline was found post PCL implementation. This may be explained by a ceiling effect, as enrollee medications with high baseline medication adherence could not improve their medication by a significant amount. In the current study, the mean PDC for the high baseline medication stratum is approximately 95% and the maximum increase in medication adherence can only be 5%, whereas those with medication adherence of 50% at baseline could increase by a substantial amount. The results suggest that the PCL did not negatively impact medication adherence for medications that had high baseline adherence among Medicaid enrollees.

Several limitations should be noted. First, medication adherence was calculated using PDC, a method that uses prescription fill data that may not reflect actual medication taking behavior. However, PDC is an objective measure of medication adherence and a measure with a lower risk of overestimating medication adherence relative to the medication possession ratio.[104] Second, the specific components of the prescription label that were modified by each pharmacy or pharmacy organization were unknown and may differ by pharmacy site. It is unclear how each modified component of the prescription drug labels affected medication adherence. Further investigation and examination will be needed for a better understanding of the effect of each modified component of the PCL. Third, this study only accounted for the number of concurrent medications and daily dosing frequency as time-varying covariates. There may be other confounders unrelated to the number of concurrent medications and daily dosing frequency that can vary over time and were not controlled for at the baseline in this study. For example, if the disease severity changes over time and affects medication adherence, there could be omitted variable bias. However, no differential effects are expected between the treatment and control groups as a result of this bias. Fourth, regression to the mean may occur as the study only measured medication adherence based on two periods. However, the study used a comparison group, which offers some protection against bias caused by regression to the mean. [104,108] The sensitivity analysis that used the pre-post difference in medication adherence as the dependent variable [104] demonstrated robust results, confirming the difference-in-difference approach used to estimate the effects of the PCL. Future research may adopt trajectory analysis to characterize patient populations by medication adherence patterns, including pre- and post-periods to provide richer information about the heterogenous effects of PCL. [109] Lastly, this study may be limited in generalizability because it only included pharmacies within certain Wisconsin counties that implemented the PCL and the study included only Medicaid patients with sufficient prescription medication fill history and days of supply. Therefore, findings may not be applicable when the intervention is scaled up or to the entire Wisconsin Medicaid population.

5.5 Conclusion

The introduction of patient-centered prescription drug labeling has a heterogenous effect on Medicaid enrollee medications with varying baseline adherence. We observed different effects between enrollee medications with low medication adherence at baseline and enrollee medications with high baseline medication adherence. Future research should examine the reasons for the heterogeneous effects of PCL on enrollee medications with different levels of baseline adherence.

5.6 Figures and Tables

Figure 5.1 Study sample

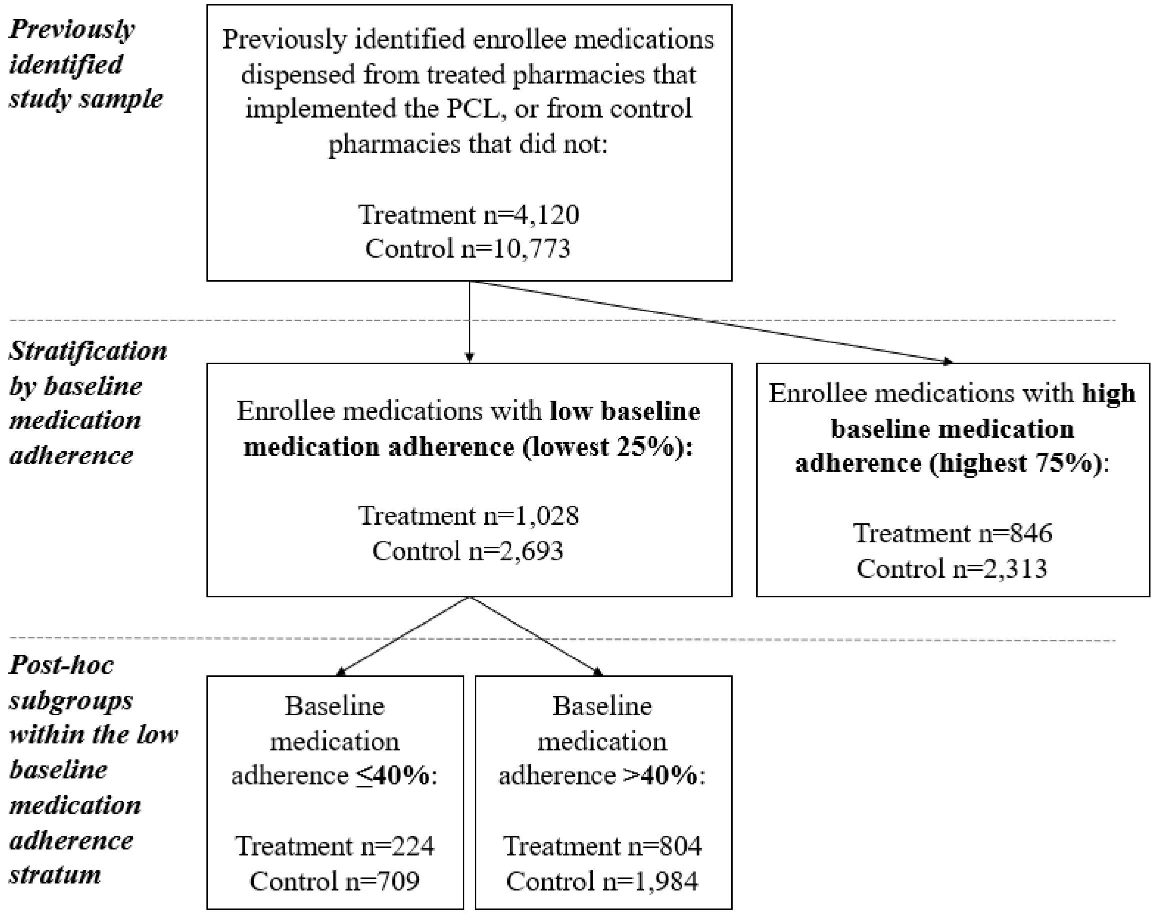

Previously identified study sample
Previously identified enrollee medications dispensed from treated pharmacies that implemented the PCL, or from control pharmacies that did not:
Treatment n=4,120
Control n=10,773
Stratification by baseline medication adherence
Enrollee medications with low baseline medication adherence (lowest 25%):
Treatment n=1,028
Control n=2,693
Enrollee medications with high baseline medication adherence (highest 75%):
Treatment n=846
Control n=2,313
Post-hoc subgroups within the low baseline medication adherence stratum
Baseline medication adherence ≤40%:
Treatment n=224
Control n=709
Baseline medication adherence >40%:
Treatment n=804
Control n=1,984

Table 5.1 Distribution of baseline PDC, treatment versus control

	Treatment	Control
	Lowest 25% n=1,028; Lowest 25%-50% n=1,032; Highest 25-50% n=908; Highest 25% n=1,152	Lowest 25% n=2,693; Lowest 25%-50% n=2,678; Highest 25-50% n=2,248; Highest 25% n=3,154
Baseline PDC, mean (Sd.)		
Lowest 25%	53.80% (0.16)	51.76% (0.17)
Lowest 25-50%	87.10% (0.05)	87.77% (0.06)
Highest 25-50%	97.95% (0.01)	98.12% (0.01)
Highest 25%	100.00% (0.00)	100.00% (0.00)

Table 5.2 Pre-period characteristics by baseline PDC, treatment versus control pharmacies

	Pharmacy									
	Baseline PDC Lowest 25%					**Baseline PDC Above Lowest 25%**				
	Treatment (n=59)		**Control (n=119)**		P-value	**Treatment (n=60)**		**Control (n=123)**		P-value
	n	%	n	%		n	%	n	%	
Health system pharmacy	11	100.0	26	100.0		12	100.0	27	100.0	
RUCA codes										
Metropolitan	11	100.0	26	100.0		12	100.0	27	100.0	
Prescription quantity(30day-adjusted)										
≤10,000	0	0.0	7	26.9	6.918	0	0.0	7	25.9	5.385
>10,000-25,000	3	27.3	2	7.7	0.075	3	25.0	3	11.1	0.146
>25,000-50,000	3	27.3	11	42.3		4	33.3	11	40.7	
>50,000	5	45.5	6	23.1		5	41.7	6	22.2	
Community pharmacy	48	100.0	93	100.0	.	48	100.0	96	100.0	.
RUCA codes										
Metropolitan	34	70.8	65	69.9	0.013	34	70.8	68	70.8	0.000
Micropolitan	7	14.6	14	15.1	1.000	7	14.6	14	14.6	1.000
Small Town	6	12.5	12	12.9		6	12.5	12	12.5	
Rural	1	2.1	2	2.2		1	2.1	2	2.1	
Prescription quantity(30day-adjusted)										
≤10,000	6	12.5	26	28.0		6	12.5	26	27.1	
>10,000-25,000	13	27.1	12	12.9	7.357	13	27.1	14	14.6	6.106
>25,000-50,000	20	41.7	34	36.6	0.061	20	41.7	35	36.5	0.107
>50,000	9	18.8	21	22.6		9	18.8	21	21.9	

Abbreviations, RUCA: Rural Urban Commuting Area

Table 5.3 Pre-period characteristics by baseline PDC, treatment versus control enrollees

	Enrollee									
	Baseline PDC Lowest 25%					Baseline PDC Above Lowest 25%				
	Treatment (n=679)		Control (n=1,883)		P-value	Treatment (n=1,288)		Control (n=3,713)		P-value
	n	%	n	%		n	%	n	%	
Age										
18-34	169	24.9	592	31.4	0.003	336	26.1	1,171	31.5	0.005
35-44	208	30.6	547	29.0		370	28.7	1,015	27.3	
45-54	235	34.6	550	29.2		415	32.2	1,085	29.2	
55-64	63	9.3	191	10.1		164	12.7	438	11.8	
65+	4	0.6	3	0.2		3	0.2	4	0.1	
Gender										
Female	447	65.8	1,279	67.9	0.319	836	64.9	2,505	67.5	0.093
Male	232	34.2	604	32.1		452	35.1	1,208	32.5	
Race										
White, non-Hispanic	361	53.2	1,070	56.8	0.000	783	60.8	2,448	65.9	0.000
Black, non-Hispanic	244	35.9	541	28.7		355	27.6	769	20.7	
Hispanic	23	3.4	150	8.0		46	3.6	244	6.6	
Other	51	7.5	122	6.5		104	8.1	252	6.8	
RUCA codes										
Metropolitan	539	79.4	1,507	80.0	0.954	986	76.6	2,808	75.6	0.143
Micropolitan	65	9.6	182	9.7		144	11.2	376	10.1	
Small Town	50	7.4	127	6.7		113	8.8	349	9.4	
Rural	25	3.7	67	3.6		45	3.5	180	4.8	
Charlson Comorbidity Index										
0	371	54.6	1,068	56.7	0.735	738	57.3	2,262	60.9	0.014
1	190	28.0	510	27.1		333	25.9	958	25.8	
2	51	7.5	141	7.5		98	7.6	221	6.0	
≥3	67	9.9	164	8.7		119	9.2	272	7.3	
Number of concurrent medications										
≤3	199	29.3	648	34.4	0.017	419	32.5	1,445	38.9	0.000
≥4-6	252	37.1	697	37.0		457	35.5	1,396	37.6	
≥7	228	33.6	538	28.6		412	32.0	872	23.5	

Abbreviations, RUCA: Rural Urban Commuting Area

Table 5.4 Pre-period characteristics by baseline PDC, treatment versus control enrollee medications

	Enrollee Medication									
	Baseline PDC Lowest 25%					Baseline PDC Above Lowest 25%				
	Treatment (n=1,028)		Treatment (n=1,028)		P-value	Treatment (n=3,092)		Treatment (n=3,092)		P-value
	n	%	n	%		n	%	n	%	
Daily dosing frequency (times/day)										
Less than 1	68	6.6	154	5.7	0.039	122	3.9	320	4.0	0.895
≥1	641	62.4	1,586	58.9		2,035	65.8	5,337	66.1	
≥2	213	20.7	596	22.1		618	20.0	1,569	19.4	
≥3	106	10.3	357	13.3		317	10.3	854	10.6	
Therapeutic category										
ADHD	39	3.8	143	5.3	0.012	182	5.9	649	8.0	0.020
Autoimmune diseases	13	1.3	47	1.7		37	1.2	90	1.1	
Cardiovascular conditions	7	0.7	18	0.7		35	1.1	90	1.1	
Dementia	0	0.0	2	0.1		3	0.1	3	0.0	
Depression	205	19.9	540	20.1		588	19.0	1,542	19.1	
Diabetes	59	5.7	140	5.2		206	6.7	526	6.5	
Diuresis	38	3.7	87	3.2		130	4.2	309	3.8	
Gout	5	0.5	23	0.9		35	1.1	63	0.8	
Hyperlipidemia	73	7.1	141	5.2		250	8.1	658	8.1	
Hypertension	156	15.2	349	13.0		637	20.6	1,517	18.8	
Osteoporosis	60	5.8	107	4.0		53	1.7	122	1.5	
Other mental health	39	3.8	135	5.0		136	4.4	350	4.3	
Parkinson's disease	6	0.6	15	0.6		22	0.7	55	0.7	
Peptic ulcer	138	13.4	332	12.3		245	7.9	608	7.5	
Seizure	167	16.2	538	20.0		417	13.5	1,130	14.0	
Thyroid disorder	23	2.2	76	2.8		116	3.8	368	4.6	

Table 5.5 Difference-in-difference OLS regression results by baseline mean PDC

	Treatment Lowest 25% n=1,028; Above lowest 25% n=3,092			Control Lowest 25% n=2,693; Above lowest 25% n=8,080			Adjusted diff-in-diff.[a]
	Pre-period	**Post-period**	**Diff.**	**Pre-period**	**Post-period**	**Diff.**	
Mean PDC							
Lowest 25% Baseline PDC	53.80%	78.02%	24.22***	51.76%	73.78%	22.02***	2.19*
Above lowest 25% Baseline PDC	95.09%	88.06%	-7.04***	95.43%	87.54%	-7.88***	0.85

[a] Adjusted for pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, number of medications per enrollee, the therapeutic category of the medication and the number of times taking the mediation per day.
*Significant at p<0.05, ** significant at p<0.01, ***significant at p<0.001

Table 5.6 Results for sensitivity analyses

	Treatment Lowest 25% n=1,028; Above lowest 25% n=3,092	Control Lowest 25% n=2,693; Above lowest 25% n=8,080	Adjusted Diff-in-diff.
Sensitivity analysis 1[a]			
Δ proportion adherent (PDC≥80%)			
Lowest 25% Baseline PDC	59.53%***	51.36%***	8.18***
Above lowest 25% Baseline PDC	-15.98%***	-18.07%***	2.09
Sensitivity analysis 2[b]			
Δ mean PDC			
Lowest 25% Baseline PDC	24.22%***	22.02%***	3.98**
Above lowest 25% Baseline PDC	-7.04%***	-7.88%***	1.04

[a] Ordinary Least Square regression model adjusted for baseline medication adherence, pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, number of medications per enrollee, the therapeutic category of the medication and the number of times taking the mediation per day, with Y=1 if PDC≥80% or Y=0 if PDC<80% as the binary dependent variable Y.
[b] Ordinary Least Square regression model adjusted for baseline medication adherence, pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, number of medications per enrollee, the therapeutic category of the medication and the number of times taking the mediation per day, with the pre-post change in the mean PDC in treatment and control as the dependent variable Y.
*Significant at p<0.05, ** significant at p<0.01, ***significant at p<0.001

Table 5.7 Post-hoc analysis for difference-in-difference regression results: subgroups of low Baseline PDC (PDC≤ 40% or > 40%), treatment versus control

	Treatment Baseline PDC≤ 40% n=224; Baseline PDC> 40% n=804			**Control** Baseline PDC≤ 40% n=709; Baseline PDC> 40% n=1,984			**Adjusted diff-in-diff.** [a]
	Pre-period	**Post-period**	**Diff.**	**Pre-period**	**Post-period**	**Diff.**	
Mean PDC							
Baseline PDC≤ 40%	28.53%	74.51%	45.98***	28.37%	69.62%	41.25***	4.73*
Baseline PDC> 40%	60.84%	79.00%	18.15***	60.84%	75.27%	15.16***	3.00*

[a] Ordinary Least Square regression model adjusted for pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, number of medications per enrollee, the therapeutic category of the medication and the number of times taking the mediation per day.

*Significant at p<0.05, ** significant at p<0.01, ***significant at p<0.001

CHAPTER SIX: MANUSCRIPT #3

Title: Regimen Complexity and Response to Patient-centered Prescription Label Intervention Targeting Adherence to Medication among Wisconsin Medicaid Populations

Target for submission: Am J Health System Pharm, Practice Research Reports (3,500 words, 250 Abstract)

Abstract

Background:

Medication regimen complexity is associated with medication nonadherence, causing adverse clinical and economic outcomes. Patient-centered prescription drug labeling (PCL) is one approach to improve medication adherence through enhancing the clarity and readability of the prescription drug label. A PCL intervention may be beneficial for individuals with a complex medication regimen that have difficulties understanding their medication use. The study objective is to evaluate the heterogeneous effect of the PCL on medication adherence by medication regimen complexity level.

Methods:

The study used Wisconsin Medicaid pharmacy claims data to evaluate the pre-post difference in medication adherence measured by the mean proportion of days covered (PDC) between medications dispensed from pharmacies that changed the drug label and medications dispensed from pharmacies that never used the new label across strata of regimen complexity level. Ordinary least squares (OLS) difference-in-differences analyses were performed within each stratum of medication regimen complexity measured at two dimensions: the number of concurrent medications taken per enrollees and the number of times per day each medication

must be taken. Sensitivity analyses using binary PDC (PDC≥80%) as the dependent variable, with both OLS and logistic difference-in-differences models were conducted.

Results:

The mean PDC significantly improved by 2.71 percentage points for enrollees taking five or fewer concurrent medications and by 1.34 percentage points for medications taken once per day. No significant change was found for other strata with higher medication complexity levels. Sensitivity analyses showed robust results.

Conclusion:

PCL only improved adherence to chronic medications taken by Medicaid enrollees that had lower regimen complexity. Future research should examine reasons for the heterogeneous effect of PCL and develop interventions beyond label change for Medicaid enrollees with high medication regimen complexity.

6.1 Introduction

Complex medication regimens have been linked to medication nonadherence, [23,110] resulting in adverse clinical and economic impacts.[68] Patients who take more prescribed medications likely face a greater burden when it comes to understanding medication instructions and managing their medication appropriately.[71,73,111] It is also more likely for patients to miss doses of medication that they are required to take multiple times per day.[72,77,80–82] If patients are not taking medications as directed, it may severely compromise treatment outcomes.[112–114] Further complications may develop from medication non-adherence, requiring further care and spending that could have been avoided. [100,115]

Strategies that enhance the clarity and understandability of information contained in prescription drug labels reduce the cognitive burden for patients to understand information related to taking medications properly. In Wisconsin, in 2014, a research team explored the feasibility of pharmacy organizations designing and using a patient-centered prescription drug label (PCL) based on standards recommended in the US Pharmacopeia Chapter 17. The newly designed label was later implemented in 63 pharmacy sites affiliated with 5 pharmacy organizations from late 2016 to 2018. Using standards set in the US Pharmacopeia Chapter 17, the new prescription drug label aims to enhance patient understanding of how to use the medication properly following dispensing from the pharmacy.

Medication regimen complexity is a concept without universal definition and measure. Although the Medication Regimen Complexity Index (MRCI) and the Medication Complex Index (MCI) are available for use as summary indices of medication regimen complexity that incorporate several components, [23,69] studies commonly use their own definition of medication regimen complexity.[72] The number of medications used concurrently and the dosing frequency of individual medications are the most commonly used aspects of a medication regimen that are used to assess medication regimen complexity.[69]

There is limited evidence about whether and how a PCL affects medication adherence based on different levels of medication regimen complexity. Only three studies investigated the effect of prescription label modifications on medication adherence among subgroups of patients who were taking multiple medications concurrently and among those who were taking medications multiple times per day. [18,21,22]

The goal of this study was to evaluate the effect of PCL on medication adherence by different levels of medication regimen complexity. Complexity was operationalized as the number of concurrent chronic medications a patient was taking during the study pre-and post-periods as well as the number of times per day each medication must be taken. The result of this study facilitates a better understanding of whether and how a PCL may be beneficial to patients using complex medication regimens.

6.2 Methods

Study Design

The study used a pre-test-post-test, non-equivalent control group design with a difference-in-difference approach, to test for changes in medication adherence following the prescription label change. The treatment group pharmacies consisted of pharmacies that made label changes from late 2016 to 2018. Control group pharmacies never made label changes. The pre-period was defined as 365 days immediately before the changed prescription label was first used in each pharmacy in the treatment group. A 90-day lookback window prior to the beginning of the pre-period was included. The post-period was defined as the 365 days following a 90-day phase-in period after the initial use of the changed label.

Study Sample

Medicaid enrollees to include in the study cohort had to meet the following inclusion criteria: (1) were age ≥ 18 as of January 1st 2015, (2) were continuously enrolled in Medicaid for each month during the study period (January 2015 to December 2019), (3) were not dual eligible, (4) were not hospitalized for ≥ 90 days at any time during the study period, and (5) received at least one prescription medication fill for a solid oral dosage form to manage one of sixteen chronic conditions (**Appendix D1**) from one of the 63 treatment pharmacy or 124 control pharmacies.

Medicaid enrollees who met the inclusion criteria were assigned to either the treatment or control group based on their exposure to PCL. An enrollee was assigned to the treatment group if they had at least one prescription for a solid oral dosage form to manage a chronic condition filled at a PCL pharmacy during the post-period. An enrollee that had prescriptions for a solid oral dosage form to manage a chronic condition filled from a control pharmacy, but never filled at a PCL pharmacy during the post-period, was assigned to the control group.

Solid oral dosage form chronic medications dispensed to each enrollee in the treatment group were included in the treatment medications if they (1) were filled at least once during the post-period from one of the treatment pharmacies; (2) had at least two fills on two unique dates, which summed up to at least two 30-day adjusted supply during the pre-period from any pharmacy; and (3) had at least two fills on two unique dates, which summed up to at least two 30-day adjusted supplies during the post-period, with at least two 30-day adjusted supplies from the treatment pharmacy. Chronic medications that are oral solid dosage form dispensed to each enrollee in the control group were included in the control group sample if the following criteria were met: (1) were filled at least once during post-period from one of the 124 control pharmacies and were never filled from any treatment pharmacies after the PCL implementation; (2) had at least two fills on two separate dates that summed up to at least two 30-day adjusted supplies during the pre-period from any pharmacy; and (3) had at least two fills on two separate dates that summed up to at least two 30-day adjusted supplies during the post-period from any pharmacy. Each enrollee medication was attributed to the specific treatment or control pharmacy that dispensed most of their prescription fills during the post-period.

Outcome Variable

The outcome variable is medication adherence measured by the proportion of days covered (PDC). PDC is the most commonly used and recommended metric for measuring medication adherence using claims data.[88,89] PDC is a ratio consisting of the number of days that a person had a particular medication in their possession, based on fill dates and days supply of medication obtained, relative to the total number of days that a person was taking the particular medication. PDC was calculated at the medication level (i.e., same drug ingredient). Medication oversupply was accounted for by shifting the next fill date forward to the day after the days supply of medication from the previous fill was exhausted. As such, the value of PDC for a particular medication cannot exceed 1.0. PDC with adjustment for oversupply was calculated in both the pre-period and the post-period.

The timeframe used for calculating the pre-period PDC depended on whether patients had days covered by the medication supply during the 90-day lookback window, before their first drug fill in the pre-period. If at least one fill for the medication was identified during the lookback window, the entire length of the pre-period was used in the denominator to estimate the pre-period PDC. The days supply of medication remaining from the last drug fill during the lookback period on the first day of the pre-period was used in calculating the pre-period PDC. If there were no medication fills during the lookback window, the length of time a medication was used (i.e., denominator) started on the date of the first medication fill in the pre-period and continued until the end of the pre-period.

In calculating the post-period PDC, only the time period following initial exposure to an attributed pharmacy (i.e., either PCL pharmacy or control pharmacy) was used to calculate PDC. As such, the date when the medication was first filled at an attributed pharmacy was considered the first day of medication supply and the beginning of the time period in which the medication was to be used (i.e., denominator). If at least one drug fill was dispensed from the attributed pharmacy during the phase-in period, the entire post-period was used as the post-period PDC estimation timeframe, and the days supply from the latest fill in the phase-in period to the first date of the post-period was used. Otherwise, the date when the medication was first filled from the attributed pharmacy during the post-period until the last date in the post-period was used as the estimation timeframe for post-period PDC.

Stratification by Regimen Complexity Level

In this study, we assessed the complexity of medication regimens in two dimensions: the number of concurrent medications an enrollee was taking and the number of times per day each medication was taken by an enrollee. The number of concurrent medications is the number of chronic medications (listed in **Appendix D1**) of a different active ingredient taken by each enrollee that had at least two fills on a separate date with at least two 30-day supplies in the pre-period and had at least two fills on a separate date with at least two 30-day supplies in the post-period. The number of times each day that an individual medication was taken was calculated as the billed quantity of the medication that was filled divided by the days supply provided for the medication. The treatment and control group enrollee medications were categorized into two strata based on the mean number of concurrent chronic medications an enrollee was taking. For dosing frequency, enrollee medications were categorized into three groups: medications taken 1 or fewer times per day, medications 2 times per day, and medications taken 3 or more times per day.

Statistical Analysis

Descriptive statistics were used to summarize the pre-period characteristics between the treatment and control group at the pharmacy, the enrollee and the enrollee medication levels for samples stratified by different regimen complexity levels for both the number of concurrent medications and the daily dosing frequency dimensions. T-tests were used for testing the significance of pre-post differences in the mean PDC within the group.

Within each stratum of the two complexity dimensions, difference-in-differences analyses were conducted to compare medication adherence between treatment and control groups. Ordinary least squares (OLS) regression was adopted to adjust for demographic, socioeconomic, and health status variables that might be associated with medication use. Covariates were based on the Andersen Behavioral Model of Health Services Utilization along with available characteristics of members. For the predisposing factors, age, sex and race and ethnicity were included. For the enabling factors that facilitate medication use, RUCA codes of enrollee residence and pharmacy location were added as covariates. As for need factors, the Carlson Comorbidity Index and therapeutic categories of medication used were included. Additionally, pharmacy type and pharmacy Medicaid prescription quantity were also controlled for at the baseline. A therapy-related factor that could affect medication adherence, [92] the number of concurrent chronic medications or daily dosing frequency, depending on which stratification variable was used, was also adjusted for. For instance, when the sample was stratified by the number of concurrent chronic medications, daily dosing frequency was controlled for as time-varying covariates in the regression model.

To ensure the robustness of the findings, sensitivity analyses were conducted using the binary proportion adherent (PDC≥80%) measured at the medication level as the dependent variable. Both OLS and logistic regression models adjusting for the same set of covariates were performed to estimate the impact of PCL on medication adherence.

6.3 Results

The average number of concurrent medications taken by enrollees in the treatment and control groups were 6.00 and 6.92, respectively. Enrollee medications were classified into two groups based on whether an enrollee was taking five or fewer concurrent medications and six or more concurrent medications.

As shown in **Figure 6.1**, for the stratification analyses by the number of concurrent medications, the study sample contains a total of 2,927 and 7,437 enrollee medications in the treatment group and control group, respectively. As for the stratification analyses by daily dosing frequency, 3,434 enrollee medications in the treatment group and 8,835 enrollee medications in the control group were included.

For pharmacy level characteristics, there were no significant differences found between the treatment and control group in the pre-period, within any stratum of the two medication regimen complexity dimensions – concurrent medications (**Table 6.2**) or daily dosing frequency (**Table 6.3**). For enrollee level characteristics, there were significant differences between the treatment and control groups in the distribution of age and race for the six or more concurrent medication stratum (**Table 6.4**). Some differences in enrollee level characteristics between the treatment and control groups were observed within strata of daily dosing frequencies (**Table 6.5**). For the enrollee medication characteristics, there were significant differences in the distribution of therapeutic categories between the treatment and control groups for the stratum with six or more concurrent medications (**Table 6.6**) and for the stratum containing medications with one time per day dosing (**Table 6.7**).

In terms of the number of concurrent medications, the fully adjusted differences-in-difference analyses showed that the PCL significantly improved mean PDC by 2.71 percentage points (p=0.040) among enrollees using 5 or fewer concurrent medications. There was no significant impact of the PCL on medication adherence for enrollees using 6 or more concurrent medications (**Table 6.8**). In terms of daily dosing frequency, the PCL significantly improved mean PDC by 1.34 percentage points (p=0.048) for enrollee medications that were taken one or fewer times per day (**Table 6.9**). There was no significant impact of the PCL on medication adherence for enrollee medications taken 2 times per day and enrollee medications taken 3 or more times per day. The full results for the primary analyses are contained in **Appendices D2-D3**.

Results from sensitivity analyses confirmed the results from the OLS difference-in-difference models (see **Appendices D4-D7**). The adjusted difference-in-difference OLS regression results indicated a significant 9.48 percentage point (p=0.001) and 4.41 percentage point (p=0.006) improvement in proportion adherent for the five or fewer concurrent medications stratum and the one or fewer times per day daily dosing stratum, respectively, in the treatment group following implementation of PCL relative to the control group. Likewise, the second set of sensitivity analyses using difference-in-difference logistic regression showed the odds of being adherent significantly increased by 66% (p=0.001) and 26% (p=0.006) within the five or fewer concurrent medications stratum and the one or fewer times per day daily dosing stratum, respectively, in the treatment group following PCL implementation relative to the control group.

6.4 Discussion

The current study showed that PCL is effective in improving medication adherence for enrollee medications within medication regimen complexity strata that, by definition, reflect lower medication complexity. Specifically, medication adherence improved for the stratum of medications that were taken with five or fewer concurrent medications and for the stratum of medications that were taken one or fewer times per day. The findings are contrary to our hypotheses that PCL would impact medication adherence when medication regimen complexity was high.

The study provided additional evidence to the limited literature on the heterogeneous effect of PCL on medication adherence across different medication regimen complexity levels when operationalized by the number of concurrent medications used and the daily dosing frequency of each medication used. Unlike previous studies that found that a label change improves medication adherence in higher regimen complexity levels, [18,21,22] the current study showed improvements in medication adherence only for enrollee medication having low regimen complexity levels.

For enrollees who were taking six or more medications, changing prescription drug labels may not be sufficient for the patient to understand how to take medications, as the enrollee may still need to read through each new label for each medication they were taking. In this case, the cognitive burden of understanding the contents of the new PCL and implementing the new information while managing multiple medications may be very burdensome. A previous study by Kripalani and colleagues found PCL with UMS instructions increased medication adherence (defined as cumulative medication gap <0.2) among patients with more than eight medications. [18] The study further examined the effect of PCL across stratum with a higher number of concurrent medications and no difference in medication adherence was found (data not reported in tables – change in mean PDC: for ≥8 concurrent medications, +0.0074, $p=0.633$; for ≥9 concurrent medications, -0.0002, $p=0.993$; for ≥10 concurrent medications, +0.0108, $p=0.590$).

The discrepancy between the current study and the previous literature could be due to the difference in the medication adherence measure.

Results for the daily dosing frequency dimension also differ from prior studies. The label change intervention in two previous studies by Wolf and colleagues contained Universal Medication Schedule (UMS) instructions that emphasize the use of simple and clear language by providing the specific number of pills to take and a specific time to take the medications. [21,22] Wolf and colleagues found that the label change intervention improved adherence among patients with medication requiring twice daily dosing [21]and those requiring more than once-daily dosing but at the same time were older than 65 years of age and less educated. [22] The PCL in the current study did not include UMS directions at any pharmacy. Thus, the dosing directions may still be confusing for some enrollees, especially those taking medications multiple times per day. Apart from the variation in the definition of subgroups, such a difference may be associated with the discrepancies between the current study and the previous literature. Further research should directly compare the effectiveness of targeted label change interventions, such as PCL + UMS versus PCL-only, on medication adherence using similar daily dosing frequency subgroups.

Several limitations should be noted. First, the study measured medication adherence by PDC, which is based on Medicaid prescription fill data and may not reflect actual medication taking behavior. However, PDC is an objective measure of medication adherence and a measure with a lower risk of overestimating medication adherence relative to the medication possession ratio.[104] Secondly, the specific components highlighted in the USP Chapter 17 standards that were incorporated into each pharmacy organization's PCL were not known and may differ by pharmacy sites or organizations. It is unclear how each changed component on prescription drug labels affected medication adherence. Further research is needed for a deeper understanding of the effect of PCL. Thirdly, this study sample only included enrollees with an unchanged or stable medication regimen complexity for the stratified analyses. The medication regimen complexity variables may be linked to disease severity. If severity changed over time, it could affect medication adherence between treatment and control groups, resulting in omitted variable bias since the variables were only controlled at baseline. However, no differential effects would be expected between the treatment and control groups as a result of this bias. Lastly, this study may be limited in its generalizability because only specific pharmacies within certain Wisconsin counties implemented the PCL and the study included only Medicaid patients with sufficient fill history and days of supply. Therefore, findings may not be applicable when the intervention is scaled up to the entire Wisconsin Medicaid population.

6.5 Conclusion

The study did not find PCL improve adherence to chronic medications taken by Medicaid enrollees that had higher medication regimen complexity. The heterogeneous effect found in this study differed from previous research. Future research should examine reasons for the heterogeneous effect of PCL and explore possible interventions to improve medication adherence for Medicaid enrollees with high medication regimen complexity.

6.6 Figures and Tables

Figure 6.1 Study samples

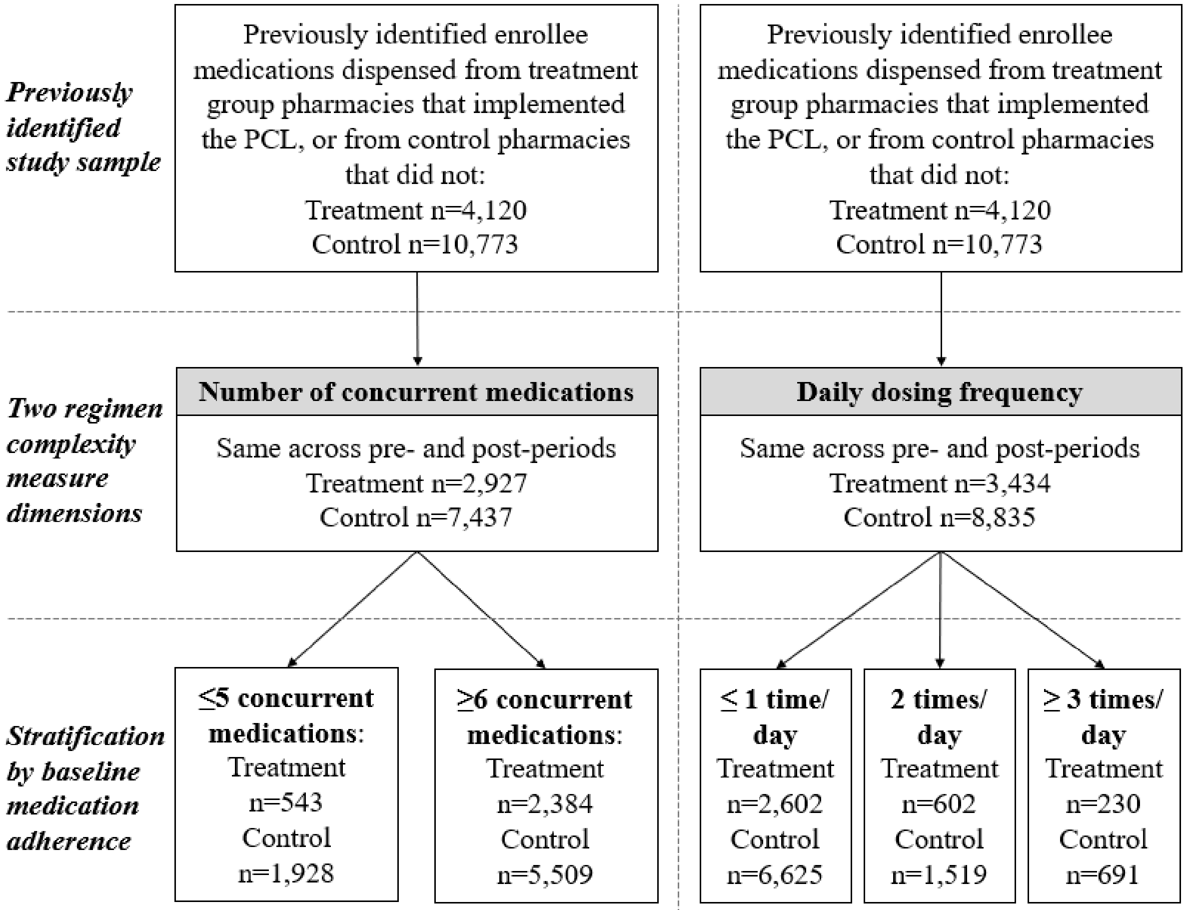

Previously identified study sample
Previously identified enrollee medications dispensed from treatment group pharmacies that implemented the PCL, or from control pharmacies that did not:
Treatment n=4,120
Control n=10,773
Previously identified enrollee medications dispensed from treatment group pharmacies that implemented the PCL, or from control pharmacies that did not:
Treatment n=4,120
Control n=10,773
Two regimen complexity measure dimensions
Number of concurrent medications
Same across pre- and post-periods
Treatment n=2,927
Control n=7,437
Daily dosing frequency
Same across pre- and post-periods
Treatment n=3,434
Control n=8,835
Stratification by baseline medication adherence
≤5 concurrent medications:
Treatment n=543
Control n=1,928
≥6 concurrent medications:
Treatment n=2,384
Control n=5,509
≤ 1 time/ day
Treatment n=2,602
Control n=6,625
2 times/ day
Treatment n=602
Control n=1,519
≥ 3 times/ day
Treatment n=230
Control n=691

Table 6.1 Distribution of regimen complexity levels, treatment versus control

	Treatment		Control	
	Same number of concurrent medications pre-and post-periods: n=2,927 Same number of concurrent medications pre-and post-period :n=3,434		Same number of concurrent medications pre-and post-periods: n=7,437 Same number of concurrent medications pre-and post-period :n=8,835	
Number of concurrent medications per enrollee				
Mean (Sd.)	6.92	(3.57)	6.00	(3.38)
Median (IQR)	7	(5)	5	(5)
Daily dosing frequency				
Mean (Sd.)	1.32	(1.00)	1.35	(1.01)
Median (IQR)	1	(0)	1	(1)

Table 6.2 Pre-period characteristics of pharmacies, treatment versus control, by number of concurrent medications

	Pharmacy									
	Number of medications ≤ 5					Number of medications ≥ 6				
	Treatment (n=59)		Control (n=119)		P-value	Treatment (n=60)		Control (n=123)		P-value
	n	%	n	%		n	%	n	%	
Health system pharmacy	11	100.0	26	100.0		13	100.0	27	100.0	
RUCA codes										
Metropolitan	11	100.0	26	100.0	.	13	100.0	27	100.0	.
Prescription quantity(30day-adjusted)										
≤10,000	0	0.0	7	26.9	0.163	0	0.0	7	25.9	0.094
>10,000-25,000	2	18.2	2	7.7		4	30.8	3	11.1	
>25,000-50,000	4	36.4	11	42.3		4	30.8	11	40.7	
>50,000	5	45.5	6	23.1		5	38.5	6	22.2	
Community pharmacy	48	100.0	94	100.0		47	100.0	94	100.0	
RUCA codes										
Metropolitan	30	69.8	66	70.2	0.995	33	70.2	66	70.2	1.000
Micropolitan	7	16.3	14	14.9		7	14.9	14	14.9	
Small Town	5	11.6	12	12.8		6	12.8	12	12.8	
Rural	1	2.3	2	2.1		1	2.1	2	2.1	
Prescription quantity(30day-adjusted)										
≤10,000	6	14.0	26	27.7	0.282	6	12.8	26	27.7	0.092
>10,000-25,000	9	20.9	13	13.8		12	25.5	12	12.8	
>25,000-50,000	19	44.2	34	36.2		20	42.6	35	37.2	
>50,000	9	20.9	21	22.3		9	19.1	21	22.3	

Abbreviations, RUCA: Rural Urban Commuting Area

Table 6.3. Pre-period characteristics of pharmacies, treatment versus control pharmacies, by daily dosing frequency

	Pharmacy														
	≤ 1 time per day					2 times per day					≥ 3 times per day				
	Treatment (n=61)		Control (n=123)		P-value	Treatment (n=57)		Control (n=120)		P-value	Treatment (n=47)		Control (n=114)		P-value
	n	n	n	%		n	%	n	%		n	%	n	%	
Health system pharmacy	13	100.0	27	100.0		11	100.0	25	100.0		7	100.0	26	100.0	
RUCA codes															
Metropolitan	13	100.0	27	100.0		11	100.0	25	100.0		7	100.0	26	100.0	
Prescription quantity(30day-adjusted)															
≤10,000	0	0.0	7	25.9	0.094	0	0.0	7	28.0	0.103	0	0.0	7	26.9	0.209
>10,000-25,000	4	30.8	3	11.1		2	18.2	1	4.0		0	0.0	2	7.7	
>25,000-50,000	4	30.8	11	40.7		4	36.4	11	44.0		3	42.9	11	42.3	
>50,000	5	38.5	6	22.2		5	45.5	6	24.0		4	57.1	6	23.1	
Health system pharmacy	48	100.0	96	100.0		46	100.0	95	100.0		40	100.0	88	100.0	
RUCA codes															
Metropolitan	34	70.8	68	70.8	1.000	33	71.7	67	70.5	0.995	28	70.0	60	68.2	0.996
Micropolitan	7	14.6	14	14.6		6	13.0	14	14.7		6	15.0	14	15.9	
Small Town	6	12.5	12	12.5		6	13.0	12	12.6		5	12.5	12	13.6	
Rural	1	2.1	2	2.1		1	2.2	2	2.1		1	2.5	2	2.3	
Prescription quantity(30day-adjusted)															
≤10,000	6	12.5	26	27.1	0.107	6	13.0	26	27.4	0.125	6	15.0	26	29.5	0.204
>10,000-25,000	13	27.1	14	14.6		12	26.1	13	13.7		8	20.0	9	10.2	
>25,000-50,000	20	41.7	35	36.5		19	41.3	35	36.8		17	42.5	32	36.4	
>50,000	9	18.8	21	21.9		9	19.6	21	22.1		9	22.5	21	23.9	

Abbreviations, RUCA: Rural Urban Commuting Area

Table 6.4 Pre-period characteristics of enrollees, treatment versus control, by number of concurrent medications

	Enrollee									
	Number of medications ≤ 5					Number of medications ≥ 6				
	Treatment (n=400)		Control (n=1,422)		P-value	Treatment (n=645)		Control (n=1,620)		P-value
	n	%	n	%		n	%	n	%	
Age										
18-34	148	37.0	594	41.8	0.175	132	20.5	414	25.6	**0.013**
35-44	123	30.8	351	24.7		177	27.4	466	28.8	
45-54	91	22.8	334	23.5		249	38.6	527	32.5	
55-64	37	9.2	139	9.8		84	13.0	211	13.0	
65+	1	0.2	4	0.3		3	0.5	2	0.1	
Gender										
Female	247	61.8	936	65.8	0.132	417	64.7	1,072	66.2	0.491
Male	153	38.2	486	34.2		228	35.3	548	33.8	
Race										
White, non-Hispanic	271	67.8	944	66.4	0.013	366	56.7	993	61.3	**0.000**
Black, non-Hispanic	87	21.8	267	18.8		209	32.4	403	24.9	
Hispanic	10	2.5	94	6.6		21	3.3	122	7.5	
Other	32	8.0	117	8.2		49	7.6	102	6.3	
RUCA codes										
Metropolitan	283	70.8	1,044	73.4	0.664	507	78.6	1,282	79.1	0.168
Micropolitan	41	10.2	144	10.1		72	11.2	157	9.7	
Small Town	51	12.8	161	11.3		50	7.8	113	7.0	
Rural	25	6.2	73	5.1		16	2.5	68	4.2	
Charlson Comorbidity Index										
0	316	79.0	1,087	76.4	0.753	294	45.6	794	49.0	0.182
1	63	15.8	253	17.8		192	29.8	491	30.3	
2	11	2.8	41	2.9		64	9.9	144	8.9	
≥3	10	2.5	41	2.9		95	14.7	191	11.8	

Abbreviations, RUCA: Rural Urban Commuting Area

Table 6.5 Pre-period characteristics of enrollees, treatment versus control, by daily dosing frequency

	Enrollee														
	≤ 1 time per day					2 times per day					≥ 3 times per day				
	Treatment (n=1,272)		Control (n=3,582)		P-value	Treatment (n=480)		Control (n=1,282)		P-value	Treatment (n=207)		Control (n=618)		P-value
	n	%	n	%		n	%	n	%		n	%	n	%	
Age															
18-34	294	23.1	1,045	29.2	**0.001**	105	21.9	370	28.9	**0.009**	58	28.0	179	29.0	0.774
35-44	374	29.4	963	26.9		132	27.5	359	28.0		64	30.9	203	32.8	
45-54	436	34.3	1,120	31.3		170	35.4	399	31.1		63	30.4	165	26.7	
55-64	163	12.8	448	12.5		72	15.0	154	12.0		22	10.6	71	11.5	
65+	5	0.4	6	0.2		1	0.2	0	0.0		0	0	0	0	
Gender															
Female	820	64.5	2,399	67.0	0.104	303	63.1	830	64.7	0.528	144	69.6	397	64.2	0.163
Male	452	35.5	1,183	33.0		177	36.9	452	35.3		63	30.4	221	35.8	
Race															
White, non-Hispanic	723	56.8	2,265	63.2	**0.000**	291	60.6	845	65.9	**0.000**	148	71.5	420	68.0	**0.004**
Black, non-Hispanic	403	31.7	823	23.0		136	28.3	259	20.2		43	20.8	112	18.1	
Hispanic	46	3.6	245	6.8		18	3.8	95	7.4		1	0.5	44	7.1	
Other	100	7.9	249	7.0		35	7.3	83	6.5		15	7.2	42	6.8	
RUCA codes															
Metropolitan	986	77.5	2,749	76.7	0.424	369	76.9	980	76.4	0.623	156	75.4	473	76.5	0.089
Micropolitan	136	10.7	355	9.9		56	11.7	134	10.5		31	15.0	60	9.7	
Small Town	102	8.0	311	8.7		36	7.5	119	9.3		12	5.8	59	9.5	
Rural	48	3.8	1,045	29.2		19	4.0	49	3.8		8	3.9	26	4.2	
Charlson Comorbidity Index															
0	712	56.0	2,126	59.4	**0.011**	233	48.5	660	51.5	0.622	111	53.6	328	53.1	0.785
1	332	26.1	952	26.6		146	30.4	364	28.4		62	30.0	179	29.0	
2	104	8.2	229	6.4		40	8.3	113	8.8		12	5.8	49	7.9	
≥3	124	9.7	275	7.7		61	12.7	145	11.3		22	10.6	62	10.0	
Number of concurrent medications															
≤3	398	31.3	1,379	38.5	**0.000**	98	20.4	338	26.4	**0.000**	51	24.6	173	28.0	0.173
≥4-6	466	36.6	1,360	38.0		167	34.8	511	39.9		69	33.3	230	37.2	
≥7	408	32.1	843	23.5		215	44.8	433	33.8		87	42.0	215	34.8	

Abbreviations, RUCA: Rural Urban Commuting Area

Table 6.6 Pre-period characteristics of enrollee medications, treatment versus control, by number of concurrent medications

	Enrollee Medication									
	Number of medications ≤ 5					**Number of medications ≥ 6**				
	Treatment (n=543)		**Control (n=1,928)**		P-value	**Treatment (n=2,384)**		**Control (n=5,509)**		P-value
	n	%	n	%		n	%	n	%	
Daily dosing frequency (times/day)										
Less than 1	30	5.5	97	5.0		101	4.2	235	4.3	
≥1	347	63.9	1,280	66.4	0.682	1,525	64.0	3,509	63.7	0.782
≥2	107	19.7	342	17.7		511	21.4	1,153	20.9	
≥3	59	10.9	209	10.8		247	10.4	612	11.1	
Therapeutic category										
ADHD	59	10.9	232	12.0		85	3.6	289	5.2	
Autoimmune diseases	4	0.7	12	0.6	0.872	34	1.4	85	1.5	**0.024**
Cardiovascular conditions	3	0.6	6	0.3		29	1.2	69	1.3	
Dementia	0	0.0	1	0.1		3	0.1	4	0.1	
Depression	124	22.8	396	20.5		431	18.1	982	17.8	
Diabetes	20	3.7	70	3.6		188	7.9	424	7.7	
Diuresis	19	3.5	54	2.8		111	4.7	230	4.2	
Gout	4	0.7	13	0.7		29	1.2	51	0.9	
Hyperlipidemia	29	5.3	143	7.4		209	8.8	443	8.0	
Hypertension	75	13.8	300	15.6		469	19.7	1,027	18.6	
Osteoporosis	14	2.6	47	2.4		59	2.5	106	1.9	
Other mental health	19	3.5	47	2.4		104	4.4	287	5.2	
Parkinson's disease	1	0.2	5	0.3		26	1.1	45	0.8	
Peptic ulcer	51	9.4	182	9.4		217	9.1	450	8.2	
Seizure	84	15.5	280	14.5		326	13.7	833	15.1	
Thyroid disorder	37	6.8	140	7.3		64	2.7	184	3.3	

Table 6.7 Pre-period characteristics of enrollee medications, treatment versus control, by daily dosing frequency

	Enrollee Medication														
	≤ 1 time per day					2 times per day					≥ 3 times per day				
	Treatment (n=2,602)		Control (n=6,625)		P-value	Treatment (n=602)		Control (n=1,519)		P-value	Treatment (n=230)		Control (n=691)		P-value
	n	%	n	%		n	%	n	%		n	%	n	%	
Therapeutic category															
ADHD	108	4.2	385	5.8	**0.003**	49	8.1	163	10.7	0.113	17	7.4	60	8.7	0.290
Autoimmune diseases	15	0.6	48	0.7		9	1.5	23	1.5		13	5.7	21	3.0	
Cardiovascular conditions	33	1.3	67	1.0		9	1.5	32	2.1		0	0.0	1	0.1	
Dementia	2	0.1	3	0.0		1	0.2	0	0.0		0	0	0	0	
Depression	544	20.9	1,417	21.4		91	15.1	212	14.0		30	13.0	63	9.1	
Diabetes	84	3.2	221	3.3		116	19.3	254	16.7		17	7.4	65	9.4	
Diuresis	137	5.3	353	5.3		15	2.5	12	0.8		1	0.4	0	0.0	
Gout	27	1.0	57	0.9		9	1.5	13	0.9		0	0.0	4	0.6	
Hyperlipidemia	302	11.6	755	11.4		7	1.2	20	1.3		0	0.0	2	0.3	
Hypertension	625	24.0	1,443	21.8		90	15.0	236	15.5		2	0.9	14	2.0	
Osteoporosis	113	4.3	228	3.4		0	0.0	1	0.1		0	0	0	0	
Other mental health	111	4.3	272	4.1		23	3.8	64	4.2		9	3.9	29	4.2	
Parkinson's disease	11	0.4	35	0.5		7	1.2	13	0.9		2	0.9	4	0.6	
Peptic ulcer	296	11.4	693	10.5		46	7.6	131	8.6		1	0.4	1	0.1	
Seizure	69	2.7	240	3.6		129	21.4	341	22.4		138	60.0	425	61.5	
Thyroid disorder	125	4.8	408	6.2		1	0.2	4	0.3		0	0.0	2	0.3	

Table 6.8 Difference-in-difference regression results by number of concurrent medications

	Treatment By number of medications: ≤ 5 n=543; >5 n=2,384			Control By number of medications: ≤ 5 n=1,928; >5 n=5,509			Adjusted diff-in-diff. [a]	Adjusted odds ratios [b]
	Pre-period	Post-period	Diff.	Pre-period	Post-period	Diff.		
By number of concurrent medications								
Mean PDC								
≤ 5	83.09%	86.31%	3.22***	84.33%	84.85%	0.51	2.71*	
> 5	85.91%	85.88%	-0.03	85.68%	85.02%	-0.67	0.63	
Proportion adherent (PDC≥80%)								
≤ 5	66.85%	76.80%	9.95***	72.20%	72.67%	0.47	9.48***	1.66***
> 5	73.95%	74.54%	0.59	74.08%	72.97%	-1.11	1.69	1.09

[a] Ordinary Least Square regression model adjusted for pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, number of medications per enrollee, the therapeutic category of the medication and the number of times taking the mediation per day.
[b] Logistic regression model adjusted for pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, the therapeutic category of the medication and the number of times taking the mediation per day.
*Significant at p<0.05, ** significant at p<0.01, ***significant at p<0.001

Table 6.9 Difference-in-difference regression results by daily dosing frequency

	Treatment ≤ 1 time/day n=2,602; 2 times/day n=602; ≥ 3 times/day n=230			Control ≤ 1 time/day n=6,625; 2 times/day n=1,519; ≥ 3 times/day n=691			Adjusted diff -in-diff. [a]	Adjusted odds ratios [b]
	Pre-period	Post-period	Diff.	Pre-period	Post-period	Diff.		
By daily dosing frequency								
Mean PDC								
≤ 1 time per day	84.76%	85.82%	1.06	85.32%	85.04%	-0.28	1.34*	
2 times per day	83.88%	84.78%	0.90	84.14%	84.00%	-0.14	1.07	
≥ 3 times per day	87.37%	86.27%	-1.09	83.12%	83.37%	0.25	-1.35	
Proportion adherent (PDC≥80%)								
≤ 1 time per day	71.21%	74.64%	3.42**	73.69%	72.73%	-0.97	4.41**	1.26**
2 times per day	70.27%	73.59%	3.32	71.43%	71.10%	-0.33	3.71	1.21
≥ 3 times per day	76.52%	74.35%	-2.17	68.31%	70.62%	2.32	-4.50	0.79

[a] Ordinary Least Square regression model adjusted for pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, number of medications per enrollee, the therapeutic category of the medication and the number of times taking the mediation per day.
[b] Logistic regression model adjusted for pharmacy type, pharmacy Medicaid prescription quantity, RUCA codes of pharmacy location, age, gender, race, RUCA codes of enrollee's residence, Charlson Comorbidity Index, number of medications per enrollee and the therapeutic category of the medication.

*Significant at p<0.05, ** significant at p<0.01, ***significant at p<0.001

CHAPTER SEVEN: DISCUSSION AND CONCLUSION

This chapter summarizes the findings from the three manuscripts of this dissertation and discusses the impact of the Wisconsin PCL intervention on medication adherence among Medicaid enrollees.

7.1 Summary of Dissertation Findings

The dissertation evaluated the change in medication adherence among the Medicaid enrollees who used medications to manage chronic conditions following the implementation of a newly designed patient-centered prescription drug label (PCL) in 63 Wisconsin pharmacies. The PCL is based on guidelines listed in the United States Pharmacopeia (USP) Chapter 17 that emphasize optimizing the readability and clarity by organizing the information presented on the prescription drug label in a patient-centered manner.[46] By comparing medication adherence between medications that were dispensed from pharmacies that changed the prescription drug label versus medications that were filled from pharmacies that did not change the drug label, the dissertation evaluated the overall effect of PCL prescription drug label on medication adherence and its heterogeneous effect on medication adherence across varying baseline medication adherence and medication regimen complexity. The findings from this dissertation address the knowledge gap in the current literature by providing additional evidence on the effect of prescription drug label improvement among Medicaid enrollees.

The first manuscript of the dissertation found that the overall medication adherence in the treatment group improved following the implementation of PCL. A significant increase of 1.17 percentage points in the mean PDC was observed in the treatment group relative to the control group. Sensitivity analyses showed that the proportion of enrollee medications with PDC ≥ 80% also increased by 3.58 percentage points post label change and the enrollee medications in the treatment group had 20% higher odds of having PDC ≥ 80% after label change compared to the control group.

The findings from this manuscript provide empirical evidence on how the PCL label can affect medication adherence in a Wisconsin Medicaid population. Results from prior studies with interventions to improve prescription label contents that explored the impact on medication adherence were inconclusive and the effect of such intervention has never been studied among the Medicaid population. [17–22] In terms of the magnitude of change in medication adherence, the 1.17 percentage point increase from this study, which is approximately 1.4% increase from the baseline, is generally consistent with previous research on the impact of label changes with positive findings that found 1-2% improvement in medication adherence. [17,22] Results suggested PCL can be incorporated with other interventions to address medication nonadherence from multiple aspects.

Apart from the findings about the overall increase in adherence to chronic medication among the Wisconsin Medicaid population, the study also assessed the heterogeneous effect of PCL by different levels of baseline medication adherence. In manuscript#2, we found that the improvement was associated with a lower baseline medication adherence, such that the enrollee medications with baseline medication adherence in the lowest 25% of the sample had a statistically significant 2.19 percentage points increase in adherence, which is about 4% increase from the baseline, post PCL implementation. Results from a further stratified analysis within this sample with the lowest 25% medication adherence also show that the magnitude of the increase in medication adherence appears to be higher for enrollee medications with baseline adherence below or equal to 40%. No change was found in the sample with higher baseline medication adherence.

The current study, as described in manuscript#2, is one of the first studies to provide evidence that PCL may improve medication adherence for Medicaid enrollees with relatively low medication adherence at baseline. Several previous studies had investigated how other medication adherence interventions had a differential effect on those with varying baseline medication adherence. In terms of the direction, our findings were similar to previous studies that found those with lower baseline medication adherence may be more sensitive to intervention and gain a greater improvement.[26,66,67] As Medicaid enrollees were at disproportionally higher risk of low health literacy,[60] misunderstanding of prescription drug labels may be a major factor of nonadherence for enrollees with low medication adherence at baseline. In this case, PCL may serve as an effective strategy to improve medication adherence by enhancing label clarity and promoting patient understanding of prescription drug labels.

The dissertation also assessed the heterogeneous effect of PCL on medication adherence by varying medication regimen complexity levels. The results in manuscript#3 demonstrated that PCL is effective in improving medication adherence for enrollee medications within strata of medication regimen complexity levels - the number of concurrent chronic medications and the number of times per day each medication needs to be taken per day. Specifically, medication adherence saw an increase by 2.71 percentage points within the stratum of medications that were taken with five or fewer concurrent medications and by 1.34 percentage points for the stratum of medications that were taken one or less time per day. No difference was found within strata with a higher regimen complexity level.

The study, as described in manuscript#3, provided additional evidence to the limited literature on the heterogeneous effect of PCL on medication adherence by different medication regimen complexity levels as measured by the number of concurrent medications and the daily dosing frequency. However, the findings are contrary to our hypothesis and previous studies that found PCL is more effective among those with a more complex medication regimen. [18,21,22] One potential explanation may be the variation in medication adherence measures used between the current study and previous studies. Additionally, it could have resulted from the nature of the intervention. The cognitive burden of understanding drug labels may not be reduced if an individual who is taking multiple medications needs to read through each of the newly designed labels. Additionally, the language used in the dosing instructions can still be confusing as the direction of use was not modified completely in all pharmacy sites due to technical difficulties.

Detailed findings and discussions are presented in the previous chapters. Manuscript#1 in chapter four focuses on the overall effect of PCL on medication adherence. Mansucritp#2 in chapter five provides details on how PCL has heterogeneous effect on medication adherence by baseline medication adherence. Manuscript#3 in chapter six centers on the heterogeneous effect of PCL on medication adherence by regimen complexity level.

7.2 Implications

The dissertation suggests the importance of a patient-centered prescription drug label can improve medication adherence for Wisconsin Medicaid enrollees. Previous studies have found a high prevalence of medication nonadherence among Medicaid enrollees.[25,100,99,101] Based on manuscript#1 findings, the average adherence to medications for managing chronic conditions of Wisconsin Medicaid enrollees is approximately 84% during the pre-period, with more than 72% of enrollee medications considered adherent (PDC ≥ 80%). While the adherence estimates were different from the previous research that suggested high prevalence of nonadherence among Medicaid enrollees, they are comparable to other research that suggested a high medication adherence rate measured by PDC among Wisconsin Medicaid enrollees.[116] The significant but marginal increase in overall medication adherence of 1.7 percentage points could be due to the fact that the medication adherence is already quite high and there is less room for improvement.

Previous literature identified that medication adherence interventions should focus on the inclusion of populations with adherence challenges.[117,118] It is noteworthy that the overall improvement in medication adherence is associated with an increase in medication adherence among enrollee medications that had an average baseline adherence of just above 50% (manuscript#2). The findings suggested that the PCL may be particularly beneficial to those having poor adherence at baseline, potentially due to low health literacy or other reasons that prevent patients from comprehending the prescription drug labels.

Previous data from other two state Medicaid programs indicated that more than 60% of Medicaid enrollees who had at least one or more chronic conditions had multimorbidity and more than 50% had five or more long-term medications simultaneously.[119] Concurrent use of multiple medications can complex medication regimen, causing non-adherence and subsequent adverse clinical and economic impacts.[112,120] While the majority of the sample in our study had only once daily dosing, similar to estimates reported previously,[119]our estimates showed that more than half of Medicaid enrollees had five or more chronic medications during the pre-period. However, findings from manuscript#3 indicated that PCL alone is not sufficient to address the adherence challenges faced by Medicaid enrollees with a complex medication regimen. Multi-faceted and muti-level interventions in addition to the PCL that focus on prescribing decision-making, drug consultation at therapy initiation with the pharmacist as well as other behavioral and technical interventions that contain certain patient reminder functions for chronic condition management may be required to improve medication adherence for individuals with a complex medication regimen. [72,112,118]

7.3 Limitations

There are several limitations in this dissertation research that should be considered. First, the study measured medication adherence by PDC based on prescription drug claims data. However, a patient's prescription refilling behavior does not always capture the actual medication taking behavior.[96] Thus, it tends to overestimate medication adherence. However, PDC is an objective measure that can prevent the hawthorn effect and has a lower risk of overestimation when compared with the medication possession ratio.[97] Further, as this study used a pre-test-post-test, non-equivalent control group study design, the same overestimation should occur in both control and treatment groups during pre- and post-periods; threat to internal validity due to such limitation is not likely.

Second, the exposure is subject to some uncertainties. Each pharmacy's new label may have different components and variations may exist between pharmacy sites. Whether each component of the changed prescription drug labels affected patient adherence differently is unknown. For a better understanding of PCL's effects, more data may be collected and examined.

Third, other unmeasured time-varying confounders that were not recorded in the data may exist, which may cause omitted variable bias. For example, if patient disease severity changed over time and affected treatment and control groups differently, the improvement in medication adherence may be caused by such confounder and not by the PCL intervention.

However, it was not anticipated that such confounders would differ over time between treatment and control groups.

As a final point, the study may have limited generalizability. There are several reasons for this, one of which is that PCL interventions were only implemented in pharmacies located in certain counties in Wisconsin, most of which are located in metropolitan areas. It is unclear whether the intervention would be effective if it were extended to all pharmacies in the state, including those in rural areas. A second reason is due to the inclusion criteria we used to identify samples. The study only included enrollees who were continuously enrolled in Medicaid, and medications with a minimum of two fills on two unique dates, which can total up to at least two 30-day adjusted fills during both pre-period and post-period. This could have biased the sample towards a relatively stable and adherent group of individuals. The results may not apply to Medicaid enrollees who had gaps in coverage due to financial difficulties, or to those who have just started taking chronic medications.

Other limitations specific to manuscript#1 through manuscript#3 were described separately from chapter four to chapter six.

7.4 Conclusions

Medicaid enrollees tend to have low health literacy,[55,60] making them more likely to misunderstand pharmaceutical labels and not adhere to their medications. [25,99] Other characteristics associated with medication nonadherence, such multimorbidity and a complex medication regimen, are also common among Medicaid enrollees.[56,57,119] PCL is a labeling approach that aims to enhance patient understanding of prescription drug labels attached to the drug containers when prescriptions were dispensed from the pharmacy. Between late 2016 and

2018, 63 pharmacy locations in Wisconsin re-designed their drug labels with support from Wisconsin Health Literacy following the PCL guidelines contained in the USP Chapter 17. [10,46] This dissertation provides empirical evidence of how the PCL label designed based on guidelines contained in the USP Chapter 17 affects adherence to chronic medications among Wisconsin Medicaid enrollees and how the effect on medication adherence differs by baseline medication adherence and regimen complexity level.

The PCL implemented in 63 pharmacy locations in Wisconsin resulted in a small but significant increase in medication adherence among adult Medicaid enrollees who used chronic condition medications. The study also found the effect of PCL on medication adherence differs between enrollee medications with different baseline medication adherence and regimen complexity level. The main gain in medication adherence was observed among those with low medication adherence at baseline and no significant change was found for those having high baseline medication adherence. The findings from two dimensions of regimen complexity defined in this study are consistent, such that only those with fewer concurrent medications and daily dosing frequency saw a significant improvement in medication adherence. Such findings suggested medication adherence interventions beyond prescription drug packaging is needed to address the adherence challenges faced by those with complex medication regimen.

This dissertation addresses various aspects of the knowledge gap. First, using a pre-test – post-test, non-equivalent control group design, and a minimum of 2 years assessment period, this dissertation provides empirical evidence for the PCL intervention implemented in Wisconsin that has not been formally assessed before. Secondly, whether PCL or similar drug label intervention may be an effective strategy for improving medication adherence among this high-risk population has never been assessed. This dissertation focused on Medicaid enrollees, a historically vulnerable population with low-income and disadvantaged socioeconomic status, who are at greater risk of low health literacy and may benefit more from a newly designed label following the PCL approach. Using an objective and continuous medication adherence measure that provides less biased and richer information than the subjective or dichotomous adherence measures, this study found the PCL intervention is associated with an increase of 1.17 percentage points improvement in the mean PDC. Thirdly, there is limited literature addressing the heterogeneous effect of medication adherence interventions, including the PCL approach, by baseline medication adherence. The study found that the improvement in medication adherence mainly occurred among medications with low baseline medication adherence, suggesting PCL may serve as a key component for medication adherence interventions among the underprivileged Medicaid populations who were non-adherent at the baseline. This study also provided evidence for the heterogeneous effect of PCL by regimen complexity level, with findings suggesting that the PCL may not be sufficient to improve medication adherence for those with a complex medication regimen.

Future research will be needed to examine the effect of PCL by various disease conditions. As the effect of medication adherence interventions may vary by condition, [107(p)] findings specific to different conditions may better inform the clinical significance for the magnitude of the medication adherence change following PCL implementation. Additionally, a future study that examines why PCL has heterogeneous effect on medication adherence is warranted. This research should further investigate the reasons for low medication adherence for those with poor baseline medication adherence and high regimen complexity in order to develop strategies that can be adopted to effectively improve medication adherence among the subpopulations. Lastly, studies that adopt a longer evaluation period that report the trend in medication adherence may be required. Evidence from such studies will be useful to understand the patterns of mediation adherence before the intervention. The trend in mediation adherence post label change will provide richer information on how PCL intervention affects enrollees with different patterns of medication adherence. The sustainability of the PCL intervention on medication adherence may also be assessed from such studies.

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APPENDICES

Appendix A

Appendix A1. Studies on Impact of Changing of Prescription Drug Labels on Adherence

No.	Author and publication year	Study Design	Patient Population	Label Change	Adherence Outcome	Findings
1	Shrank et al (2009) [17]	Cohort study	23 745 adults with chronic diseases used Target pharmacy and 162 369 matched non-Target users in New Jersey and Minnesota	Container label ClearRx	Continuous proportion of days covered (PDC)	No change in adherence was found in new users while a small level change (-0.007) and slope change (+0.0007) and was found among prevalent users
2	Kripalani et al (2012)[18]	RCT, 2 × 2 factorial design	432 English speaking adults with coronary heart disease from community sites in Mississippi	Patient-centered prescription drug label (PCL) with UMS instructions	Dichotomous cumulative medication gap (CMG)	No difference in medication refill adherence was found between arms (usual care vs reminder postcard vs supplementary medication schedules vs both) and those with low baseline medication adherence. Medication schedule improved adherence among patients with 8+ medication.
3	Martin et al (2012)[19]	Pre-post pilot study	20 older adults from day center	PCL with UMS instructions	Self-reported adherence assessed by Adherence to Refills and Medications Scale (ARMS)	Increase in self-efficacy and medication adherence were found after 6 weeks of intervention

4	Mohan et al (2014)[20]	RCT	200 Latino diabetic patients from a clinic in Nashville Tennessee	PCL with UMS instructions	Self-reported adherence assessed by ARMS	<u>No difference</u> in self-reported adherence was found between arms (usual care vs supplementary medication schedules)
5	Wolf et al (2016) [21]	Cohort study	845 English and Spanish speaking patients from community health centers who received prescriptions in a central-filled pharmacy in northern Virginia that were diagnosed with type 2 diabetes or hypertension, with aged 30 or older and taking 2 or more oral medications	PCL with UMS instructions	Self-reported adherence assessed by Patient Medication Adherence Questionnaire (PMAQ) and pill count	<u>No difference</u> in medication adherence was found between arms (PCL vs non-PCL) Improvement in medication adherence was found in subgroups (patients with limited literacy and patients with medications requiring twice daily dosing or more)
6	Wolf et al (2020)[22]	Cohort study	676 739 English speaking type 2 diabetic adults who received 796 909 prescriptions from Walgreens pharmacy	Use of UMS instruction (tier 1-3)	Dichotomous PDC	Better adherence was found in prescriptions with strict UMS instructions (tier 1) compared to non-UMS instructions in the overall and subgroup (patients over 65 years old who were less educated requiring more than once daily dosing)
7	Sparks et al (2018) [12]	Pre-post pilot study	288 patients who used medication to treat asthma controllers, hypertension, contraception, depression in Hayat Pharmacy	Patient-centered prescription medication label	Categorical medication possession ratio (MPR)	Decrease in patients with MPR 0-50% and MPR 50%-80% and increase in those with MPR >80%

Appendix A2. Characteristics between enrollees with and without continuous Medicaid enrollment from 2015 to 2019.

	Enrollment				
	Not Continuously Enrolled		5 Year Continuously Enrolled		Chi-squared
	n	%	n	%	P-value
Age					
18-34	394,916	55.5	79,145	40.2	16067.287
35-44	128,265	18.0	41,243	20.9	0.000
45-54	98,613	13.9	39,141	19.9	
55-64	55,894	7.9	24,634	12.5	
65+	33,542	4.7	12,851	6.5	
Gender					
Female	395,748	55.6	116,926	59.3	862.048
Male	315,482	44.4	80,088	40.7	0.000
Race					
White, non-Hispanic	445,452	62.6	117,544	59.7	11219.026
Black, non-Hispanic	115,963	16.3	50,674	25.7	0.000
Other	44,698	6.3	9,799	5.0	
Hispanic	66,340	9.3	12,707	6.4	
Unknown	38,016	5.3	6,065	3.1	
More than 1 race	761	0.1	225	0.1	
Rural Urban Commuting Area Category					
Metropolitan	505,262	71.0	142,249	72.2	148.116
Micropolitan	77,248	10.9	19,830	10.1	0.000
Small Town	70,366	9.9	19,351	9.8	
Rural	58,233	8.2	15,571	7.9	
Unknown	121	0.0	13	0.0	
Charlson Comorbidity Index (Nov 2015-Oct 2016)					
0	291,014	79.7	97,396	61.8	19452.841

1	45,381	12.4	32,110	20.4	0.000
2	10,563	2.9	11,029	7.0	
≥3	18,147	5.0	16,983	10.8	

Only Medicaid enrollees continuously enrolled in Medicaid throughout the study period were studied. This is a traditional approach commonly used by research to ensure the completeness of data when medication adherence is estimated through secondary data sources. A higher proportion of female, people with older age, and people of non-Hispanic black race were seen among the 5 year continuously enrolled enrollees compared to those that are not continuously enrolled. RUCA categories are similar between two groups. Given the differences in the characteristics of between the not continuously enrolled versus the continuously enrolled population, the generalizability of our study findings may not be applied to all Wisconsin Medicaid enrollees.

Appendix B (Manuscript#1)

Appendix B1. Medications for treating or managing chronic conditions

Chronic conditions	Therapeutic categories
ADHD	ADHD stimulant; ADHD, miscellaneous
Depression	Alpha2 receptor antagonist; Antidepressants cyclic Antidepressants, miscellaneous; MAOIs; Serotonin modulators; SNRIs; SSRIs
Diabetics	Biguanides; DDP4 inhibitors; Incretin Mimetics; Meglitinides; SG2 inhibitors; Sulfonylureas; Thiazolidinediones
Hyperlipidemia	Bile acid sequestrants; Cholesterol absorption inhibitors; Fibric acid derivatives; Statins
Hypertension	ACEIs; Alpha-blocker; ARBs; Beta-blocker; Calcium Channel Blocker; Renin inhibitor
Autoimmune disease	Anti-inflammatory agents (GI); Hormones - Adrenals DMARDS; Immunomodulatory agents
Other heart conditions	Antianginal agents (non-nitrate); Antiarrhythmics Antiplatelets; Non-warfarin anticoagulant
Dementia	Acetylcholinesterase inhibitors; NMDA receptor antagonists
Diuresis	Loop diuretics; Potassium sparing diuretics; Thiazide diuretics; Thiazide-like diuretics
Gout	Antiarthritics
Osteoporosis	Bisphosphonate Hormones-Estrogens Vitamin D
Other mental health	Antimanic agents Antipsychotics-First generation Antipsychotics-Second generation
Parkinson's disease	Antiparkinsonian Agents
Peptic ulcer	Proton Pump Inhibitor
Seizure	Anticonvulsants
Thyroid disorder	Hyperparathyroid treatment- Vitamin D analogs Hypothyroid agent

Appendix B2. Difference-in-difference linear regression estimates of the effect of PCL on PDC

	Primary analysis, mean PDC, OLS	**Sensitivity analysis, proportion adherent (PDC>=80%), OLS**	**Sensitivity analysis, proportion adherent (PDC>=80%), logistic**
Treatment	-0.0022 (0.0039)	-0.0137 (0.0084)	0.9303 (0.0401)
Post-period	-0.0041 (0.0030)	-0.0071 (0.0060)	0.9642 (0.0296)
Treatment x post-period	0.0117* (0.0055)	0.0358** (0.0114)	1.2045** (0.0711)
Health system pharmacy	-0.0238*** (0.0034)	-0.0405*** (0.0069)	0.8169*** (0.0275)
Pharmacy RUCA codes (ref. Metropolitan) Micropolitan	-0.0005 (0.0057)	0.0012 (0.0120)	1.0137 (0.0651)
Small Town	-0.0246* (0.0123)	-0.0378 (0.0267)	0.8222 (0.1168)
Rural	-0.0121 (0.0064)	-0.0229 (0.0134)	0.8868 (0.0629)
Prescription quantity (30day-adjusted)	-0.0000*** (0.0000)	-0.0000*** (0.0000)	1.0000*** (0.0000)
Age	0.0012*** (0.0001)	0.0023*** (0.0003)	1.0117*** (0.0014)
Male	0.0014 (0.0027)	0.0055 (0.0055)	1.0317 (0.0294)
Race (Ref. White, non-Hispanic)			

Black, non-Hispanic	-0.0472***	-0.0905***	0.6385***
	(0.0036)	(0.0073)	(0.0226)
Hispanic	-0.0169**	-0.0319**	0.8471**
	(0.0057)	(0.0116)	(0.0484)
Other race	-0.0131**	-0.0302**	0.8527**
	(0.0051)	(0.0106)	(0.0462)
Enrollee residential RUCA codes (ref. Metropolitan)			
Micropolitan	-0.0035	-0.0059	0.9675
	(0.0058)	(0.0120)	(0.0606)
Small Town	0.0058	0.0168	1.0951
	(0.0065)	(0.0133)	(0.0782)
Rural	0.0093	0.0179	1.1042
	(0.0067)	(0.0144)	(0.0879)
CCI=1 (Ref. CCI=0)	-0.0038	-0.0082	0.9601
	(0.0031)	(0.0063)	(0.0306)
CCI=2	0.0002	0.0022	1.0136
	(0.0048)	(0.0099)	(0.0528)
CCI≥3	0.0035	0.0044	1.0228
	(0.0045)	(0.0092)	(0.0489)
Number of concurrent medications	0.0005	0.0018*	1.0086
	(0.0005)	(0.0009)	(0.0046)
Daily dosing frequency (times/day)	-0.0005*	-0.0009*	0.9960*
	(0.0002)	(0.0004)	(0.0019)
Therapeutic categories (Ref. ADHD)			
Depression	-0.0464***	-0.0925***	0.6194***
	(0.0059)	(0.0113)	(0.0385)
Diabetes	-0.0075	-0.0348*	0.8315*
	(0.0071)	(0.0145)	(0.0668)
Diuresis	0.0126	-0.0080	0.9642
	(0.0076)	(0.0162)	(0.0893)

Hyperlipidemia	-0.0003	-0.0237	0.8881
	(0.0066)	(0.0137)	(0.0693)
Hypertension	0.0139*	0.0042	1.0374
	(0.0058)	(0.0116)	(0.0694)
Other mental health	-0.0557***	-0.1058***	0.5860***
	(0.0085)	(0.0161)	(0.0474)
Peptic ulcer	-0.0717***	-0.1407***	0.4970***
	(0.0070)	(0.0135)	(0.0345)
Seizure	-0.0590***	-0.1208***	0.5463***
	(0.0062)	(0.0119)	(0.0346)
Thyroid disorder	0.0358***	0.0564***	1.5086***
	(0.0067)	(0.0143)	(0.1498)
Other	-0.0758***	-0.1480***	0.4825***
	(0.0079)	(0.0151)	(0.0364)
Constant	0.8465***	0.7282***	
	(0.0073)	(0.0146)	

Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix B3. Difference-in-difference OLS regression estimates of the effect of PCL on mean PDC, by proportion of days covered from attributed pharmacy

	Attributed Day 50%	Attributed Day 50-100%	Attributed Day 100%
Treatment	0.0202	-0.0058	-0.0037
	(0.0171)	(0.0136)	(0.0042)
Post-period	0.0354***	-0.0001	-0.0101**
	(0.0090)	(0.0095)	(0.0033)
Treatment x Post-period	0.0259	0.0239	0.0121*
	(0.0182)	(0.0181)	(0.0061)
Health system pharmacy	-0.0258**	-0.0183	-0.0225***
	(0.0096)	(0.0099)	(0.0041)
Pharmacy RUCA codes (ref. Metropolitan)	-0.0344	0.0207	0.0045
	(0.0177)	(0.0173)	(0.0066)
Small Town	0.0169	-0.1101	-0.0252
	(0.0255)	(0.0658)	(0.0137)
Rural	-0.0502*	-0.0604**	0.0010
	(0.0207)	(0.0206)	(0.0073)
Prescription quantity(30day-adjusted)	-0.0000*	-0.0000***	-0.0000*
	(0.0000)	(0.0000)	(0.0000)

Age	0.0010*	0.0012**	0.0012***
	(0.0004)	(0.0004)	(0.0001)
Male	-0.0052	-0.0084	0.0030
	(0.0090)	(0.0088)	(0.0030)
Race (Ref. White, non-Hispanic) Black, non-Hispanic	-0.0218*	-0.0680***	-0.0468***
	(0.0109)	(0.0117)	(0.0041)
Hispanic	0.0303	-0.0070	-0.0242***
	(0.0163)	(0.0171)	(0.0065)
Other race	-0.0047	-0.0466**	-0.0096
	(0.0169)	(0.0167)	(0.0056)
Enrollee residential RUCA codes (ref. Metropolitan) Micropolitan	0.0170	-0.0062	-0.0101
	(0.0141)	(0.0176)	(0.0069)
Small Town	0.0621**	0.0088	-0.0031
	(0.0198)	(0.0202)	(0.0074)
Rural	0.0405	0.0234	0.0022
	(0.0211)	(0.0213)	(0.0076)

CCI=1 (Ref. CCI=0)	-0.0205*	-0.0325**	0.0014
	(0.0095)	(0.0101)	(0.0034)
CCI=2	-0.0383*	-0.0427*	0.0086
	(0.0191)	(0.0170)	(0.0052)
CCI≥3	-0.0132	-0.0185	0.0083
	(0.0153)	(0.0142)	(0.0050)
Number of concurrent medications	-0.0004	0.0062***	-0.0002
	(0.0014)	(0.0013)	(0.0005)
Daily dosing frequency (times/day)	0.0077	-0.0008	-0.0005*
	(0.0042)	(0.0044)	(0.0002)
Therapeutic categories (Ref. ADHD)	-0.0693***	-0.0816***	-0.0331***
Depression	(0.0138)	(0.0161)	(0.0074)
Diabetes	-0.0499*	0.0045	0.0011
	(0.0254)	(0.0221)	(0.0085)
Diuresis	-0.0169	0.0167	0.0221*
	(0.0291)	(0.0266)	(0.0090)
Hyperlipidemia	0.0027	-0.0286	0.0089

	(0.0217)	(0.0217)	(0.0080)
Hypertension	-0.0249	0.0092	0.0247***
	(0.0159)	(0.0165)	(0.0073)
Other mental health	-0.0634***	-0.0731***	-0.0477***
	(0.0188)	(0.0218)	(0.0105)
Peptic ulcer	-0.0694***	-0.0985***	-0.0623***
	(0.0195)	(0.0208)	(0.0084)
Seizure	-0.0791***	-0.0721***	-0.0516***
	(0.0135)	(0.0174)	(0.0078)
Thyroid disorder	-0.0041	0.0088	0.0485***
	(0.0260)	(0.0239)	(0.0080)
Other	-0.1151***	-0.0894***	-0.0637***
	(0.0241)	(0.0231)	(0.0093)
Constant	0.8592***	0.8360***	0.8414***
	(0.0211)	(0.0224)	(0.0089)

Standard errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix B4. Sensitivity analysis: Difference-in-difference OLS regression estimates of the effect of PCL on proportion adherent (PDC≥80%), by proportion of days covered from attributed pharmacy

	Attributed Day 50%	Attributed Day 50-100%	Attributed Day 100%
Treatment	0.0238	-0.0225	-0.0159
	(0.0398)	(0.0316)	(0.0124)
Post-period	0.0495**	-0.0104	-0.0146*
	(0.0190)	(0.0188)	(0.0073)
Treatment x Post-period	0.0597	0.0425	0.0374*
	(0.0430)	(0.0423)	(0.0146)
Health system pharmacy	-0.0257	-0.0318	-0.0391**
	(0.0238)	(0.0248)	(0.0125)
Pharmacy RUCA codes (ref. Metropolitan)	-0.0921	0.0263	0.0114
	(0.0485)	(0.0470)	(0.0211)
Small Town	0.0229	-0.1786	-0.0351
	(0.0562)	(0.1104)	(0.0462)
Rural	-0.0903	-0.1082	-0.0018
	(0.0501)	(0.0594)	(0.0222)
Prescription quantity(30day-	-0.0000*	-0.0000*	-0.0000

adjusted)			
	(0.0000)	(0.0000)	(0.0000)
Age	0.0012	0.0027*	0.0022***
	(0.0011)	(0.0011)	(0.0004)
Male	-0.0161	-0.0149	0.0090
	(0.0227)	(0.0229)	(0.0093)
Race (Ref. White, non-Hispanic)	-0.0408	-0.1192***	-0.0912***
Black, non-Hispanic	(0.0279)	(0.0282)	(0.0127)
Hispanic	0.0897*	-0.0197	-0.0497*
	(0.0352)	(0.0449)	(0.0205)
Other	-0.0446	-0.1190**	-0.0172
	(0.0480)	(0.0427)	(0.0186)
Enrollee residential RUCA codes (ref. Metropolitan) Micropolitan	0.0272	-0.0277	-0.0143
	(0.0350)	(0.0466)	(0.0213)
Small Town	0.0991*	-0.0064	0.0070
	(0.0458)	(0.0615)	(0.0219)
Rural	0.0543	0.0724	0.0041

	(0.0606)	(0.0562)	(0.0253)
CCI=1 (Ref. CCI=0)	-0.0470	-0.0594*	0.0017
	(0.0241)	(0.0255)	(0.0103)
CCI=2	-0.0644	-0.0674	0.0157
	(0.0513)	(0.0431)	(0.0174)
CCI≥3	-0.0191	-0.0643	0.0149
	(0.0399)	(0.0357)	(0.0176)
Number of concurrent medications	-0.0031	0.0114***	0.0011
	(0.0034)	(0.0033)	(0.0016)
Daily dosing frequency (times/day)	0.0134	-0.0015	-0.0010*
	(0.0090)	(0.0095)	(0.0004)
Therapeutic categories (Ref. ADHD)	-0.1566***	-0.1638***	-0.0628***
Depression	(0.0307)	(0.0361)	(0.0158)
Diabetes	-0.1092	0.0003	-0.0186
	(0.0570)	(0.0487)	(0.0202)
Diuresis	-0.0904	0.0110	0.0116
	(0.0759)	(0.0576)	(0.0212)

Hyperlipidemia	0.0016	-0.0644	-0.0060
	(0.0542)	(0.0520)	(0.0180)
Hypertension	-0.0740	-0.0174	0.0280
	(0.0388)	(0.0389)	(0.0165)
Other mental health	-0.1722***	-0.1515***	-0.0777***
	(0.0418)	(0.0448)	(0.0216)
Peptic ulcer	-0.1806***	-0.1948***	-0.1167***
	(0.0457)	(0.0451)	(0.0180)
Seizure	-0.1811***	-0.1489***	-0.1006***
	(0.0301)	(0.0370)	(0.0170)
Thyroid disorder	-0.0544	0.0122	0.0846***
	(0.0697)	(0.0542)	(0.0184)
Other	-0.2271***	-0.1756***	-0.1235***
	(0.0525)	(0.0496)	(0.0201)
Constant	0.8187***	0.7138***	0.7086***
	(0.0474)	(0.0549)	(0.0232)

Standard errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix B5. Sensitivity analysis: Difference-in-difference logistic regression estimates (odds ratios) of the effect of PCL on proportion adherent (PDC≥80%), by proportion of days covered from attributed pharmacy

	Attributed Day 50%	Attributed Day 50-100%	Attributed Day 100%
Treatment			
	1.1033	0.8925	0.9184
	(0.1994)	(0.1147)	(0.0441)
Post-period			
	1.2732**	0.9521	0.9267*
	(0.1165)	(0.0852)	(0.0326)
Treatment x Post-period			
	1.5132	1.2218	1.2178**
	(0.3783)	(0.2139)	(0.0798)
Health system pharmacy			
	0.8681	0.8596	0.8200***
	(0.0876)	(0.0791)	(0.0331)
Pharmacy RUCA codes (Ref. Metropolitan) Micropolitan			
	0.6076*	1.1452	1.0724
	(0.1322)	(0.2136)	(0.0813)
Small Town			
	1.1741	0.4420	0.8304
	(0.5285)	(0.2204)	(0.1341)
Rural			
	0.6218*	0.5985*	0.9924
	(0.1464)	(0.1219)	(0.0810)
Prescription quantity(30day-			

adjusted)			
	1.0000^{**}	1.0000^{***}	1.0000^{*}
	(0.0000)	(0.0000)	(0.0000)
Age			
	1.0063	1.0125^{**}	1.0118^{***}
	(0.0045)	(0.0039)	(0.0016)
Male			
	0.9226	0.9311	1.0527
	(0.0884)	(0.0793)	(0.0338)
Race (Ref. White, non-Hispanic)			
Black, non-Hispanic			
	0.8222	0.5782^{***}	0.6304^{***}
	(0.0898)	(0.0601)	(0.0256)
Hispanic			
	1.5728^{**}	0.9007	0.7708^{***}
	(0.2710)	(0.1398)	(0.0511)
Other			
	0.8113	0.5718^{***}	0.9111
	(0.1492)	(0.0892)	(0.0560)
Enrollee residential RUCA codes (Ref.Metropolitan) Micropolitan			
	1.1871	0.8756	0.9223
	(0.2046)	(0.1481)	(0.0700)
Small Town			
	1.6915^{*}	0.9753	1.0408
	(0.4518)	(0.1985)	(0.0849)

Rural			
	1.3426	1.4590	1.0249
	(0.3870)	(0.3325)	(0.0933)
CCI=1 (Ref. CCI=0)			
	0.7920*	0.7581**	1.0101
	(0.0795)	(0.0707)	(0.0367)
CCI=2			
	0.7333	0.7344	1.0909
	(0.1372)	(0.1178)	(0.0638)
CCIâ‰¥3			
	0.9061	0.7385*	1.0829
	(0.1460)	(0.1048)	(0.0586)
Number of concurrent medications(pre-period)			
	0.9844	1.0553***	1.0052
	(0.0139)	(0.0135)	(0.0053)
Daily dosing frequency (times/day)			
	1.0683	0.9913	0.9955*
	(0.0490)	(0.0409)	(0.0019)
Therapeutic category (Ref. ADHD) Depression			
	0.4158***	0.4597***	0.7218***
	(0.0688)	(0.0710)	(0.0553)
Diabetes			
	0.5272*	1.0082	0.9089
	(0.1515)	(0.2392)	(0.0855)
Diuresis			

	0.5843	1.0521	1.0768
	(0.2072)	(0.2901)	(0.1151)
Hyperlipidemia			
	0.9983	0.7255	0.9784
	(0.3191)	(0.1683)	(0.0892)
Hypertension			
	0.6272*	0.9172	1.1913*
	(0.1238)	(0.1619)	(0.0967)
Other mental health			
	0.3922***	0.4833***	0.6771***
	(0.0806)	(0.0977)	(0.0669)
Peptic ulcer			
	0.3751***	0.4059***	0.5611***
	(0.0800)	(0.0762)	(0.0469)
Seizure			
	0.3718***	0.4930***	0.6070***
	(0.0600)	(0.0803)	(0.0477)
Thyroid disorder			
	0.6973	1.1053	1.8195***
	(0.2313)	(0.3235)	(0.2095)
Other			
	0.3087***	0.4401***	0.5460***

Exponentiated coefficients; Standard errors in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix C (Manuscript#2)

Appendix C1. Medications for treating or managing chronic conditions

Chronic conditions	Therapeutic categories
ADHD	ADHD stimulant; ADHD, miscellaneous
Depression	Alpha2 receptor antagonist; Antidepressants cyclic Antidepressants, miscellaneous; MAOIs; Serotonin modulators; SNRIs; SSRIs
Diabetics	Biguanides; DDP4 inhibitors; Incretin Mimetics; Meglitinides; SG2 inhibitors; Sulfonylureas; Thiazolidinediones
Hyperlipidemia	Bile acid sequestrants; Cholesterol absorption inhibitors; Fibric acid derivatives; Statins
Hypertension	ACEIs; Alpha-blocker; ARBs; Beta-blocker; Calcium Channel Blocker; Renin inhibitor
Autoimmune disease	Anti-inflammatory agents (GI); Hormones - Adrenals DMARDS; Immunomodulatory agents
Other heart conditions	Antianginal agents (non-nitrate); Antiarrhythmics Antiplatelets; Non-warfarin anticoagulant
Dementia	Acetylcholinesterase inhibitors; NMDA receptor antagonists
Diuresis	Loop diuretics; Potassium sparing diuretics; Thiazide diuretics; Thiazide-like diuretics
Gout	Antiarthritics
Osteoporosis	Bisphosphonate Hormones-Estrogens Vitamin D
Other mental health	Antimanic agents Antipsychotics-First generation Antipsychotics-Second generation
Parkinson's disease	Antiparkinsonian Agents
Peptic ulcer	Proton Pump Inhibitor
Seizure	Anticonvulsants
Thyroid disorder	Hyperparathyroid treatment- Vitamin D analogs Hypothyroid agent

Appendix C2. Difference-in-difference OLS regression estimates of the effect of PCL on mean PDC, by baseline PDC

	Lowest 25% Baseline PDC	Above lowest 25% Baseline PDC
Post-period	0.2202***	-0.0788***
	(0.0061)	(0.0030)
Treatment	0.0148*	-0.0018
	(0.0066)	(0.0021)
Treatment x Post-period	0.0219*	0.0085
	(0.0110)	(0.0061)
Health system pharmacy	-0.0180**	-0.0017
	(0.0065)	(0.0036)
Pharmacy RUCA codes (Ref. Metropolitan) Micropolitan	-0.0211	0.0062
	(0.0126)	(0.0058)
Small Town	-0.0677*	-0.0013
	(0.0295)	(0.0119)
Rural	-0.0185	0.0050
	(0.0149)	(0.0068)
Prescription quantity(30day-adjusted)	-0.0000	-0.0000
	(0.0000)	(0.0000)
Age	0.0009**	0.0005***
	(0.0003)	(0.0002)
Male	0.0020	-0.0029
	(0.0055)	(0.0030)
Race (Ref. White, non-Hispanic) Black, non-Hispanic	-0.0196**	-0.0216***
	(0.0065)	(0.0040)
Hispanic	-0.0029	-0.0073

	(0.0107)	(0.0056)
Other	-0.0024	-0.0049
	(0.0098)	(0.0061)
Enrollee residential RUCA codes (Ref. Metropolitan) Micropolitan	0.0057	-0.0029
	(0.0121)	(0.0058)
Small Town	0.0179	-0.0126
	(0.0156)	(0.0067)
Rural	0.0457**	-0.0083
	(0.0155)	(0.0078)
CCI=1 (Ref. CCI=0)	-0.0016	-0.0013
	(0.0062)	(0.0032)
CCI=2	0.0013	0.0071
	(0.0098)	(0.0055)
CCI≥3	-0.0038	0.0047
	(0.0090)	(0.0052)
Number of concurrent medications	-0.0005	-0.0011*
	(0.0009)	(0.0005)
Daily dosing frequency (times/day)	-0.0004***	0.0035**
	(0.0001)	(0.0014)
Therapeutic categories (Ref. ADHD) Depression	0.0017	-0.0231***
	(0.0137)	(0.0050)
Diabetes	0.0421*	-0.0023
	(0.0166)	(0.0059)
Diuresis	0.0615***	0.0188**
	(0.0174)	(0.0062)
Hyperlipidemia	0.0638***	-0.0006

	(0.0158)	(0.0056)
Hypertension	0.0589***	0.0118*
	(0.0143)	(0.0051)
Other mental health	-0.0049	-0.0370***
	(0.0175)	(0.0074)
Peptic ulcer	-0.0008	-0.0222***
	(0.0146)	(0.0059)
Seizure	-0.0061	-0.0271***
	(0.0139)	(0.0055)
Thyroid disorder	0.0994***	0.0284***
	(0.0178)	(0.0053)
Other	-0.0154	-0.0329***
	(0.0159)	(0.0071)
Constant	0.4836***	0.9480***
	(0.0164)	(0.0076)

Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix C3. Subgroup analysis of medication with lowest 25% baseline PDC: difference-in-difference OLS regression estimates of the effect of PCL on mean PDC

	PDC<=40%, Lowest 25% Baseline PDC	**PDC>40%, Lowest 25% Baseline PDC**
Post-period	0.4124***	0.1516***
	(0.0121)	(0.0069)
Treatment	0.0003	0.0044
	(0.0085)	(0.0056)
Treatment x Post-period	0.0473*	0.0300*
	(0.0236)	(0.0127)
Health system pharmacy	-0.0195	-0.0103
	(0.0130)	(0.0077)
Pharmacy RUCA codes (Ref. Metropolitan) Micropolitan	0.0134	-0.0143
	(0.0266)	(0.0148)
Small Town	-0.1457**	-0.0340
	(0.0469)	(0.0303)
Rural	0.0049	-0.0229
	(0.0275)	(0.0179)
Prescription quantity(30day-adjusted)	0.0000	-0.0000
	(0.0000)	(0.0000)
Age	-0.0008	0.0008**
	(0.0006)	(0.0003)
Male	0.0117	0.0006
	(0.0111)	(0.0064)
Race (Ref. White, non-Hispanic) Black, non-Hispanic	0.0054	-0.0233**
	(0.0132)	(0.0077)
Hispanic	-0.0007	0.0009

	(0.0201)	(0.0124)
Other	-0.0005	-0.0163
	(0.0239)	(0.0117)
Enrollee residential RUCA codes (Ref. Metropolitan) Micropolitan	-0.0270	-0.0028
	(0.0252)	(0.0148)
Small Town	0.0261	0.0072
	(0.0265)	(0.0184)
Rural	-0.0277	0.0336*
	(0.0411)	(0.0171)
CCI=1 (Ref. CCI=0)	0.0008	0.0020
	(0.0121)	(0.0072)
CCI=2	0.0086	-0.0023
	(0.0221)	(0.0108)
CCI≥3	0.0341	-0.0084
	(0.0188)	(0.0106)
Number of concurrent medications	-0.0008	-0.0007
	(0.0017)	(0.0010)
Daily dosing frequency (times/day)	-0.0002**	0.0033
	(0.0001)	(0.0028)
Therapeutic categories (Ref. ADHD) Depression	-0.0034	-0.0118
	(0.0216)	(0.0144)
Diabetes	-0.0044	0.0162
	(0.0326)	(0.0173)
Diuresis	0.0047	0.0394*
	(0.0351)	(0.0178)
Hyperlipidemia	0.0431	0.0381*

	(0.0289)	(0.0163)
Hypertension	0.0028	0.0402^{**}
	(0.0258)	(0.0148)
Other mental health	0.0017	-0.0125
	(0.0276)	(0.0192)
Peptic ulcer	-0.0164	-0.0012
	(0.0231)	(0.0152)
Seizure	-0.0087	-0.0202
	(0.0218)	(0.0148)
Thyroid disorder	0.0730^{*}	0.0608^{***}
	(0.0347)	(0.0181)
Other	-0.0427	-0.0054
	(0.0257)	(0.0166)
Constant	0.3138^{***}	0.5774^{***}
	(0.0289)	(0.0183)

Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix C4. Sensitivity analysis: Difference-in-difference OLS regression estimates of the effect of PCL on proportion adherent (PDC≥80%), by baseline PDC

	Lowest 25% Baseline PDC	**Lower50% of Lowest 25% Baseline PDC**
Post-period	0.5136***	-0.1807***
	(0.0112)	(0.0062)
Treatment	-0.0002	-0.0044
	(0.0049)	(0.0052)
Treatment x Post-period	0.0818***	0.0209
	(0.0207)	(0.0123)
Health system pharmacy	-0.0078	0.0001
	(0.0120)	(0.0072)
Pharmacy RUCA codes (Ref. Metropolitan)		
Micropolitan	-0.0336	0.0118
	(0.0252)	(0.0120)
Small Town	-0.1004*	0.0023
	(0.0501)	(0.0265)
Rural	-0.0041	0.0042
	(0.0271)	(0.0141)
Prescription quantity(30day-adjusted)	0.0000	-0.0000
	(0.0000)	(0.0000)
Age	0.0005	0.0011***
	(0.0005)	(0.0003)
Male	0.0060	-0.0033
	(0.0105)	(0.0060)
Race (Ref. White, non-Hispanic) Black, non-Hispanic	-0.0129	-0.0416***
	(0.0121)	(0.0081)
Hispanic	-0.0100	-0.0080

	(0.0210)	(0.0115)
Other	-0.0124	-0.0080
	(0.0192)	(0.0116)
Enrollee residential RUCA codes (Ref. Metropolitan)		
Micropolitan	0.0037	-0.0011
	(0.0235)	(0.0116)
Small Town	-0.0001	-0.0113
	(0.0280)	(0.0136)
Rural	0.0626*	-0.0078
	(0.0305)	(0.0170)
CCI=1 (Ref. CCI=0)	-0.0113	-0.0003
	(0.0113)	(0.0065)
CCI=2	-0.0028	0.0196
	(0.0184)	(0.0109)
CCI≥3	-0.0134	0.0081
	(0.0177)	(0.0108)
Number of concurrent medications	0.0011	-0.0021*
	(0.0017)	(0.0010)
Daily dosing frequency (times/day)	-0.0006***	0.0066**
	(0.0001)	(0.0025)
Therapeutic categories (Ref. ADHD) Depression	-0.0110	-0.0393***
	(0.0204)	(0.0099)
Diabetes	0.0156	-0.0106
	(0.0264)	(0.0124)
Diuresis	0.0228	0.0245
	(0.0286)	(0.0130)
Hyperlipidemia	0.0422	-0.0086

	(0.0251)	(0.0118)
Hypertension	0.0309	0.0146
	(0.0223)	(0.0102)
Other mental health	-0.0130	-0.0645***
	(0.0262)	(0.0140)
Peptic ulcer	-0.0027	-0.0350**
	(0.0220)	(0.0118)
Seizure	-0.0247	-0.0500***
	(0.0206)	(0.0107)
Thyroid disorder	0.1199***	0.0534***
	(0.0283)	(0.0112)
Other	-0.0192	-0.0621***
	(0.0237)	(0.0140)
Constant	-0.0249	0.9440***
	(0.0267)	(0.0150)

Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix C5. Sensitivity analysis: OLS estimates of the effect of PCL on change in mean PDC, by baseline PDC

	Lowest 25% Baseline PDC	Above 25% Baseline PDC
Treatment	0.0398**	0.0104
	(0.0122)	(0.0064)
Health system pharmacy	-0.0116	0.0027
	(0.0129)	(0.0065)
Pharmacy RUCA codes (Ref. Metropolitan) Micropolitan	-0.0253	0.0155
	(0.0243)	(0.0107)
Small Town	-0.1314*	0.0108
	(0.0513)	(0.0197)
Rural	-0.0305	0.0140
	(0.0298)	(0.0122)
Prescription quantity(30day-adjusted)	0.0000	0.0000
	(0.0000)	(0.0000)
Age	0.0006	0.0010***
	(0.0005)	(0.0003)
Male	0.0046	-0.0095
	(0.0110)	(0.0056)
Race (Ref. White, non-Hispanic) Black, non-Hispanic	-0.0286*	-0.0268***
	(0.0130)	(0.0074)
Hispanic	-0.0111	-0.0124
	(0.0211)	(0.0106)
Other	-0.0215	-0.0035
	(0.0200)	(0.0113)
Enrollee residential RUCA codes (Ref.Metropolitan)	-0.0049	-0.0065

Micropolitan		
	(0.0229)	(0.0106)
Small Town	0.0117	-0.0280*
	(0.0303)	(0.0121)
Rural	0.0335	-0.0123
	(0.0338)	(0.0139)
CCI=1 (Ref. CCI=0)	-0.0007	0.0037
	(0.0121)	(0.0060)
CCI=2	0.0017	0.0114
	(0.0195)	(0.0102)
CCI≥3	0.0010	0.0120
	(0.0186)	(0.0098)
Number of concurrent medications(pre-period)	-0.0010	-0.0034***
	(0.0018)	(0.0009)
Daily dosing frequency (times/day)	-0.0004***	0.0053*
	(0.0001)	(0.0026)
Therapeutic category (Ref. ADHD) Depression	-0.0136	-0.0361***
	(0.0228)	(0.0092)
Diabetes	0.0251	0.0068
	(0.0283)	(0.0109)
Diuresis	0.0601*	0.0372***
	(0.0288)	(0.0112)
Hyperlipidemia	0.0684**	0.0081
	(0.0260)	(0.0103)
Hypertension	0.0563*	0.0298**
	(0.0241)	(0.0092)
Other mental health	-0.0090	-0.0639***
	(0.0292)	(0.0138)

Peptic ulcer	-0.0022	-0.0225*
	(0.0243)	(0.0110)
Seizure	-0.0214	-0.0409***
	(0.0231)	(0.0101)
Thyroid disorder	0.1176***	0.0594***
	(0.0289)	(0.0097)
Other	-0.0282	-0.0579***
	(0.0262)	(0.0134)
Baseline medication adherence	-0.8554***	-0.6746***
	(0.0279)	(0.0350)
Constant	0.6447***	0.5489***
	(0.0320)	(0.0367)
Observations	3721	11172

Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix D (Manuscript#3)

Appendix D1. Medications for treating or managing chronic conditions

Chronic conditions	Therapeutic categories
ADHD	ADHD stimulant; ADHD, miscellaneous
Depression	Alpha2 receptor antagonist; Antidepressants cyclic Antidepressants, miscellaneous; MAOIs; Serotonin modulators; SNRIs; SSRIs
Diabetics	Biguanides; DDP4 inhibitors; Incretin Mimetics; Meglitinides; SG2 inhibitors; Sulfonylureas; Thiazolidinediones
Hyperlipidemia	Bile acid sequestrants; Cholesterol absorption inhibitors; Fibric acid derivatives; Statins
Hypertension	ACEIs; Alpha-blocker; ARBs; Beta-blocker; Calcium Channel Blocker; Renin inhibitor
Autoimmune disease	Anti-inflammatory agents (GI); Hormones - Adrenals DMARDS; Immunomodulatory agents
Other heart conditions	Antianginal agents (non-nitrate); Antiarrhythmics Antiplatelets; Non-warfarin anticoagulant
Dementia	Acetylcholinesterase inhibitors; NMDA receptor antagonists
Diuresis	Loop diuretics; Potassium sparing diuretics; Thiazide diuretics; Thiazide-like diuretics
Gout	Antiarthritics
Osteoporosis	Bisphosphonate Hormones-Estrogens Vitamin D
Other mental health	Antimanic agents Antipsychotics-First generation Antipsychotics-Second generation
Parkinson's disease	Antiparkinsonian Agents
Peptic ulcer	Proton Pump Inhibitor
Seizure	Anticonvulsants
Thyroid disorder	Hyperparathyroid treatment- Vitamin D analogs Hypothyroid agent

Appendix D2. Difference-in-difference OLS regression estimates of the effect of PCL on mean PDC, by number of concurrent medications

	≤5 concurrent medications	≥6 concurrent medications
Treatment	-0.0129	-0.0014
	(0.0109)	(0.0075)
Post-period	0.0051	-0.0067
	(0.0064)	(0.0046)
Treatment x Post-period	0.0271*	0.0063
	(0.0132)	(0.0094)
Health system pharmacy	-0.0296**	-0.0200**
	(0.0098)	(0.0077)
Pharmacy RUCA codes (Ref. Metropolitan) Micropolitan	-0.0108	0.0047
	(0.0169)	(0.0111)
Small Town	-0.0337	-0.0275
	(0.0336)	(0.0259)
Rural	-0.0149	-0.0189
	(0.0168)	(0.0139)
Prescription quantity(30day-adjusted)	-0.0000	-0.0000
	(0.0000)	(0.0000)
Age	0.0009*	0.0011***
	(0.0004)	(0.0003)
Male	-0.0028	0.0008
	(0.0081)	(0.0061)
Race (Ref. White, non-Hispanic) Black, non-Hispanic	-0.0728***	-0.0380***
	(0.0122)	(0.0082)
Hispanic	-0.0272	-0.0235
	(0.0167)	(0.0127)

Other race	0.0286*	-0.0276*
	(0.0121)	(0.0126)
Enrollee residential RUCA codes (Ref. Metropolitan) Micropolitan	0.0089	-0.0028
	(0.0173)	(0.0115)
Small Town	0.0101	0.0131
	(0.0163)	(0.0140)
Rural	0.0230	0.0266*
	(0.0186)	(0.0129)
CCI=1 (Ref. CCI=0)	0.0028	-0.0009
	(0.0097)	(0.0065)
CCI=2	0.0102	-0.0034
	(0.0244)	(0.0099)
CCI≥3	0.0399	-0.0011
	(0.0210)	(0.0094)
Daily dosing frequency (times/day)	0.0093**	0.0020
	(0.0035)	(0.0020)
Therapeutic categories (Ref. ADHD) Depression	-0.0611***	-0.0279**
	(0.0124)	(0.0103)
Diabetes	-0.0285	0.0060
	(0.0192)	(0.0119)
Diuresis	-0.0014	0.0297*
	(0.0215)	(0.0127)
Hyperlipidemia	-0.0036	0.0142
	(0.0151)	(0.0112)
Hypertension	-0.0108	0.0337**
	(0.0140)	(0.0104)
Other mental health	-0.0747**	-0.0415**

	(0.0259)	(0.0134)
Peptic ulcer	-0.1343***	-0.0369**
	(0.0164)	(0.0119)
Seizure	-0.1038***	-0.0432***
	(0.0158)	(0.0109)
Thyroid disorder	0.0135	0.0498***
	(0.0135)	(0.0117)
Other	-0.1142***	-0.0487***
	(0.0224)	(0.0131)
Constant	0.8712***	0.8368***
	(0.0183)	(0.0152)

Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix D3. Difference-in-difference OLS regression estimates of the effect of PCL on mean PDC, by daily dosing frequency

	≤1 time daily dosing frequency	2 times daily dosing frequency	≥3 times daily dosing frequency
Treatment	-0.0079	-0.0161	0.0410**
	(0.0048)	(0.0108)	(0.0151)
Post-period	-0.0031	-0.0021	0.0025
	(0.0037)	(0.0079)	(0.0121)
Treatment x Post-period	0.0134*	0.0107	-0.0135
	(0.0068)	(0.0150)	(0.0220)
Health system pharmacy	-0.0257***	-0.0141	-0.0389**
	(0.0043)	(0.0092)	(0.0137)
Pharmacy RUCA codes (Ref. Metropolitan) Micropolitan	0.0019	0.0005	-0.0451
	(0.0070)	(0.0147)	(0.0252)
Small Town	-0.0144	-0.0538	-0.0230
	(0.0149)	(0.0338)	(0.0316)
Rural	-0.0056	0.0083	-0.0364
	(0.0080)	(0.0164)	(0.0249)
Prescription quantity(30day-adjusted)	-0.0000	-0.0000***	-0.0000
	(0.0000)	(0.0000)	(0.0000)
Age	0.0018***	0.0005	-0.0006
	(0.0002)	(0.0004)	(0.0005)
Male	-0.0015	0.0125	0.0245*
	(0.0033)	(0.0073)	(0.0116)
Race (Ref. White, non-Hispanic) Black, non-Hispanic	-0.0494***	-0.0427***	-0.0883***
	(0.0045)	(0.0100)	(0.0158)
Hispanic	-0.0216**	0.0011	-0.0266
	(0.0071)	(0.0136)	(0.0259)

Other race	-0.0247***	-0.0160	0.0134
	(0.0063)	(0.0145)	(0.0189)
Enrollee residential RUCA codes (Ref. Metropolitan) Micropolitan	-0.0061	-0.0022	-0.0186
	(0.0072)	(0.0152)	(0.0254)
Small Town	0.0014	-0.0104	0.0408
	(0.0081)	(0.0166)	(0.0245)
Rural	0.0019	0.0271	-0.0038
	(0.0083)	(0.0178)	(0.0312)
CCI=1 (Ref. CCI=0)	-0.0029	-0.0179*	-0.0023
	(0.0038)	(0.0084)	(0.0134)
CCI=2	-0.0010	-0.0266*	0.0126
	(0.0057)	(0.0132)	(0.0200)
CCI≥3	-0.0012	-0.0025	-0.0015
	(0.0055)	(0.0120)	(0.0197)
Number of concurrent medications	0.0019***	0.0041***	0.0003
	(0.0006)	(0.0011)	(0.0018)
Therapeutic categories (Ref. ADHD) Depression	-0.0368***	-0.0802***	0.0076
	(0.0083)	(0.0138)	(0.0224)
Diabetes	-0.0207	-0.0037	0.0326
	(0.0118)	(0.0128)	(0.0243)
Diuresis	0.0168	-0.0125	0.1730***
	(0.0097)	(0.0272)	(0.0352)
Hyperlipidemia	0.0012	-0.0089	0.0564
	(0.0088)	(0.0274)	(0.0642)
Hypertension	0.0196*	-0.0154	0.0695*
	(0.0082)	(0.0127)	(0.0346)
Other mental health	-0.0612***	-0.0485*	0.0191

	(0.0118)	(0.0201)	(0.0286)
Peptic ulcer	-0.0673***	-0.0949***	0.1472**
	(0.0093)	(0.0165)	(0.0562)
Seizure	-0.0587***	-0.0813***	-0.0239
	(0.0122)	(0.0125)	(0.0197)
Thyroid disorder	0.0408***	-0.0112	0.0408
	(0.0088)	(0.0765)	(0.0419)
Other	-0.0770***	-0.1098***	-0.0432
	(0.0103)	(0.0209)	(0.0328)
Constant	0.8105***	0.8838***	0.8968***
	(0.0098)	(0.0181)	(0.0278)

Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix D4. Sensitivity analysis: Difference-in-difference OLS regression estimates of the effect of PCL on proportion adherent (PDC≥80%), by number of concurrent medications

	≤5 concurrent medications	≥6 concurrent medications
Treatment	-0.0550*	-0.0045
	(0.0246)	(0.0160)
Post-period	0.0047	-0.0111
	(0.0134)	(0.0094)
Treatment x Post-period	0.0948***	0.0169
	(0.0282)	(0.0188)
Health system pharmacy	-0.0574**	-0.0328*
	(0.0196)	(0.0151)
Pharmacy RUCA codes (Ref. Metropolitan) Micropolitan	-0.0188	0.0120
	(0.0348)	(0.0234)
Small Town	-0.0284	-0.0427
	(0.0686)	(0.0510)
Rural	-0.0372	-0.0277
	(0.0363)	(0.0286)
Prescription quantity(30day-adjusted)	-0.0000	-0.0000
	(0.0000)	(0.0000)
Age	0.0017*	0.0022***
	(0.0008)	(0.0006)
Male	0.0022	-0.0004
	(0.0164)	(0.0123)
Race (Ref. White, non-Hispanic) Black, non-Hispanic	-0.1396***	-0.0810***
	(0.0234)	(0.0162)
Hispanic	-0.0753*	-0.0345
	(0.0360)	(0.0237)

Other race	0.0398	-0.0616*
	(0.0260)	(0.0266)
Enrollee residential RUCA codes (Ref. Metropolitan) Micropolitan	0.0174	-0.0169
	(0.0352)	(0.0240)
Small Town	0.0316	0.0161
	(0.0355)	(0.0288)
Rural	0.0527	0.0483
	(0.0381)	(0.0271)
CCI=1 (Ref. CCI=0)	0.0088	-0.0036
	(0.0198)	(0.0129)
CCI=2	0.0282	0.0003
	(0.0471)	(0.0203)
CCI≥3	0.0738	-0.0027
	(0.0476)	(0.0189)
Daily dosing frequency (times/day)	0.0184**	0.0019
	(0.0064)	(0.0038)
Therapeutic categories (Ref. ADHD) Depression	-0.1351***	-0.0462*
	(0.0243)	(0.0206)
Diabetes	-0.0686	-0.0010
	(0.0423)	(0.0249)
Diuresis	-0.0469	0.0422
	(0.0471)	(0.0261)
Hyperlipidemia	-0.0171	0.0114
	(0.0317)	(0.0232)
Hypertension	-0.0540	0.0532*
	(0.0298)	(0.0210)
Other mental health	-0.1148*	-0.0682**

	(0.0513)	(0.0254)
Peptic ulcer	-0.2694***	-0.0610**
	(0.0315)	(0.0233)
Seizure	-0.1928***	-0.0817***
	(0.0298)	(0.0216)
Thyroid disorder	0.0264	0.0705**
	(0.0282)	(0.0257)
Other	-0.2153***	-0.0837***
	(0.0420)	(0.0253)
Constant	0.7785***	0.7046***
	(0.0364)	(0.0306)

Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix D5. Sensitivity analysis: Difference-in-difference OLS regression estimates of the effect of PCL on proportion adherent (PDC≥80%), by daily dosing frequency

	≤1 time daily dosing frequency	2 times daily dosing frequency	≥3 times daily dosing frequency
Treatment	-0.0299*	-0.0373	0.0857*
	(0.0133)	(0.0246)	(0.0361)
Post-period	-0.0103	-0.0045	0.0234
	(0.0076)	(0.0142)	(0.0224)
Treatment x Post-period	0.0441**	0.0371	-0.0450
	(0.0160)	(0.0283)	(0.0405)
Health system pharmacy	-0.0439***	-0.0241	-0.0668*
	(0.0119)	(0.0224)	(0.0310)
Pharmacy RUCA codes (Ref. Metropolitan) Micropolitan	0.0056	-0.0134	-0.0818
	(0.0198)	(0.0390)	(0.0561)
Small Town	-0.0240	-0.0669	-0.0923
	(0.0445)	(0.0794)	(0.1053)
Rural	-0.0025	-0.0237	-0.1022
	(0.0225)	(0.0423)	(0.0635)
Prescription quantity(30day-adjusted)	-0.0000	-0.0000***	-0.0000
	(0.0000)	(0.0000)	(0.0000)
Age	0.0033***	0.0012	-0.0010
	(0.0005)	(0.0009)	(0.0013)
Male	0.0007	0.0384*	0.0428
	(0.0096)	(0.0177)	(0.0266)
Race (Ref. White, non-Hispanic) Black, non-Hispanic	-0.0896***	-0.0900***	-0.1739***
	(0.0125)	(0.0248)	(0.0377)
Hispanic	-0.0390	0.0055	-0.0411
	(0.0202)	(0.0345)	(0.0623)

Other race	-0.0496*	-0.0234	0.0120
	(0.0204)	(0.0342)	(0.0498)
Enrollee residential RUCA codes (Ref. Metropolitan) Micropolitan	-0.0058	0.0033	-0.0248
	(0.0194)	(0.0391)	(0.0599)
Small Town	0.0016	0.0166	0.1078
	(0.0220)	(0.0419)	(0.0595)
Rural	0.0015	0.0714	0.0520
	(0.0261)	(0.0440)	(0.0623)
CCI=1 (Ref. CCI=0)	-0.0006	-0.0461*	-0.0108
	(0.0104)	(0.0206)	(0.0317)
CCI=2	0.0038	-0.0631	0.0082
	(0.0179)	(0.0336)	(0.0468)
CCI≥3	-0.0000	-0.0138	0.0033
	(0.0176)	(0.0287)	(0.0477)
Number of concurrent medications	0.0040**	0.0077**	-0.0024
	(0.0015)	(0.0028)	(0.0043)
Therapeutic categories (Ref. ADHD) Depression	-0.0784***	-0.1667***	0.0025
	(0.0176)	(0.0322)	(0.0480)
Diabetes	-0.0658*	-0.0187	0.0590
	(0.0268)	(0.0308)	(0.0566)
Diuresis	-0.0032	-0.0597	0.3201***
	(0.0224)	(0.0827)	(0.0826)
Hyperlipidemia	-0.0260	-0.0172	-0.0200
	(0.0198)	(0.0564)	(0.2059)
Hypertension	0.0107	-0.0544	0.1315
	(0.0184)	(0.0307)	(0.0806)
Other mental health	-0.1099***	-0.1121*	0.0136

	(0.0242)	(0.0440)	(0.0699)
Peptic ulcer	-0.1356***	-0.1731***	0.2528
	(0.0199)	(0.0370)	(0.1594)
Seizure	-0.1303***	-0.1605***	-0.0406
	(0.0263)	(0.0284)	(0.0408)
Thyroid disorder	0.0638**	-0.0824	0.2154***
	(0.0198)	(0.2142)	(0.0421)
Other	-0.1638***	-0.1533***	-0.0927
	(0.0221)	(0.0417)	(0.0698)
Constant	0.6667***	0.7951***	0.8148***
	(0.0242)	(0.0421)	(0.0636)

Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix D6. Sensitivity analysis: Difference-in-difference logistic regression estimates of the effect of PCL on proportion adherent (PDC≥80%), by number of concurrent medications

	≤5 concurrent medications	≥6 concurrent medications
Treatment	0.7514*	0.9727
	(0.0927)	(0.0829)
Post-period	1.0256	0.9432
	(0.0741)	(0.0468)
Treatment x Post-period	1.6612***	1.0941
	(0.2525)	(0.1096)
Health system pharmacy	0.7418**	0.8450*
	(0.0738)	(0.0646)
Pharmacy RUCA codes (Ref. Metropolitan) Micropolitan	0.9032	1.0805
	(0.1747)	(0.1418)
Small Town	0.8311	0.7904
	(0.3369)	(0.2359)
Rural	0.8009	0.8549
	(0.1629)	(0.1331)
Prescription quantity(30day-adjusted)	1.0000	1.0000
	(0.0000)	(0.0000)
Age	1.0091*	1.0117***
	(0.0041)	(0.0032)
Male	1.0053	1.0005
	(0.0875)	(0.0657)
Race (Ref. White, non-Hispanic) Black, non-Hispanic	0.5184***	0.6569***
	(0.0578)	(0.0539)
Hispanic	0.6818*	0.8301

	(0.1174)	(0.1003)
Other race	1.2744	0.7232*
	(0.2046)	(0.0961)
Enrollee residential RUCA codes (Ref. Metropolitan) Micropolitan	1.0993	0.9081
	(0.2138)	(0.1159)
Small Town	1.2175	1.0995
	(0.2444)	(0.1753)
Rural	1.3812	1.3504
	(0.3189)	(0.2296)
CCI=1 (Ref. CCI=0)	1.0468	0.9806
	(0.1113)	(0.0673)
CCI=2	1.1587	1.0022
	(0.3132)	(0.1098)
CCI≥3	1.4800	0.9857
	(0.4192)	(0.0984)
Daily dosing frequency (times/day)	1.1477*	1.0082
	(0.0780)	(0.0191)
Therapeutic categories (Ref. ADHD) Depression	0.4680***	0.7874*
	(0.0710)	(0.0860)
Diabetes	0.6498	0.9986
	(0.1654)	(0.1350)
Diuresis	0.7534	1.2776
	(0.2124)	(0.1913)
Hyperlipidemia	0.9285	1.0709
	(0.1975)	(0.1370)
Hypertension	0.7234	1.3734**
	(0.1350)	(0.1616)

Other mental health	0.5188*	0.7123**
	(0.1385)	(0.0911)
Peptic ulcer	0.2604***	0.7329*
	(0.0449)	(0.0887)
Seizure	0.3375***	0.6687***
	(0.0609)	(0.0748)
Thyroid disorder	1.3062	1.5860**
	(0.2832)	(0.2621)
Other	0.3388***	0.6610**
	(0.0731)	(0.0844)

Exponentiated coefficients; Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix D7. Sensitivity analysis: Difference-in-difference logistic regression estimates of the effect of PCL on proportion adherent (PDC≥80%), by daily dosing frequency

	≤ 1 time daily dosing frequency	2 times daily dosing frequency	≥3 times daily dosing frequency
Treatment	0.8532* (0.0589)	0.8254 (0.1027)	1.5698* (0.3107)
Post-period	0.9469 (0.0383)	0.9771 (0.0709)	1.1225 (0.1234)
Treatment x Post-period	1.2624** (0.1067)	1.2138 (0.1766)	0.7885 (0.1721)
Health system pharmacy	0.7978*** (0.0478)	0.8802 (0.0981)	0.7078* (0.1063)
Pharmacy RUCA codes (Ref. Metropolitan) Micropolitan	1.0432 (0.1161)	0.9384 (0.1969)	0.6456 (0.1849)
Small Town	0.8810 (0.2144)	0.7134 (0.3105)	0.6023 (0.3221)
Rural	0.9877 (0.1223)	0.8819 (0.2015)	0.5608 (0.1900)
Prescription quantity(30day-adjusted)	1.0000 (0.0000)	1.0000*** (0.0000)	1.0000 (0.0000)
Age	1.0175*** (0.0024)	1.0063 (0.0045)	0.9946 (0.0064)
Male	1.0057 (0.0509)	1.2261* (0.1145)	1.2360 (0.1683)
Race (Ref. White, non-Hispanic) Black, non-Hispanic	0.6306*** (0.0399)	0.6446*** (0.0772)	0.4445*** (0.0752)
Hispanic	0.8124*	1.0213	0.8239

	(0.0834)	(0.1818)	(0.2382)
Other race	0.7670*	0.8794	1.0667
	(0.0806)	(0.1529)	(0.2919)
Enrollee residential RUCA codes (Ref. Metropolitan) Micropolitan	0.9656	1.0216	0.8985
	(0.1011)	(0.2084)	(0.2693)
Small Town	1.0097	1.0989	1.8573
	(0.1220)	(0.2485)	(0.6358)
Rural	1.0103	1.5105	1.3310
	(0.1493)	(0.4076)	(0.4438)
CCI=1 (Ref. CCI=0)	0.9987	0.7943*	0.9388
	(0.0550)	(0.0823)	(0.1465)
CCI=2	1.0209	0.7320	1.0492
	(0.0998)	(0.1223)	(0.2524)
CCI≥3	0.9960	0.9370	1.0156
	(0.0936)	(0.1396)	(0.2369)
Number of concurrent medications	1.0210**	1.0399**	0.9876
	(0.0082)	(0.0153)	(0.0207)
Therapeutic categories (Ref. ADHD) Depression	0.6672***	0.4111***	1.0102
	(0.0629)	(0.0745)	(0.2608)
Diabetes	0.7090*	0.8831	1.4003
	(0.1004)	(0.1675)	(0.4478)
Diuresis	0.9973	0.7006	1.0000
	(0.1256)	(0.3272)	(.)
Hyperlipidemia	0.8786	0.9173	0.8947
	(0.0963)	(0.3446)	(0.9748)
Hypertension	1.0848	0.7253	2.2619
	(0.1111)	(0.1357)	(1.3216)

Other mental health	0.5787***	0.5345**	1.0730
	(0.0694)	(0.1250)	(0.4156)
Peptic ulcer	0.5113***	0.4011***	1.0000
	(0.0526)	(0.0794)	(.)
Seizure	0.5274***	0.4289***	0.8144
	(0.0672)	(0.0710)	(0.1733)
Thyroid disorder	1.5901***	0.6240	1.0000
	(0.2025)	(0.6620)	(.)
Other	0.4530***	0.4363***	0.6289
	(0.0501)	(0.0965)	(0.2107)

Exponentiated coefficients; Standard errors in parentheses
* p < 0.05, ** p < 0.01, *** p < 0.001