HEALTHCARE AND MEDICATION ADHERENCE AMONG OLDER ADULTS WITH CHRONIC DISEASES

A Dissertation

by

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ABSTRACT

Older adults account for almost one-third of all medications prescribed in the US. Of special concerns are the high rates of medication non-adherence in this population. Understanding the drivers of the medication non-adherence among the older population can inform effective public health interventions. This dissertation is divided into three separate sections, and each section examines different determinants of the medication non-adherence.

The first section used systematic literature review and meta-analysis to describe the prevalence of medication non-adherence and overview the association between patient-provider relationship and medication non-adherence among community-dwelling older adults. Ten studies were included in this review. The mean prevalence rate of medication non-adherence was 33%. Information exchange was positively associated with medication non-adherence, but discussion about barriers was negatively associated with medication non-adherence.

The second section used multiple linear mixed-effects models to examine the long-term impacts of the Chronic Disease Self-Management Program (CDSMP) on medication non-adherence in older adults. Medication adherence did not improve significantly at the 6-month follow-up assessment (p=0.518) but improved significantly at the 12-month follow-up assessment (p=0.021). Among those with major depression at the baseline assessment, the short-term improvements in depression (p=0.002) and self-

rated health (p=0.045) were associated with improved medication adherence at the 12-month follow-up assessment.

The third section used structural equation modeling to examine the causal paths between poverty, patient attitudes, and cost-related medication non-adherence (CRN). Six percent of the participants reported CRN in the past 12-months. The final model showed a good-to-fair fit. As hypothesized, the effects of poverty on CRN was mediated through the medication affordability, access to healthcare, and overall patient satisfaction.

Medication non-adherence is a complex problem that is rooted in multitudes of inter-related factors, and the three sections have examined multiple modifiable factors, suggesting several points of intervention for improving medication adherence among older adults. We call for more senior-friendly public health interventions that address the modifiable barriers (e.g., patient-provider relationship, depression, self-rated health, and patient attitudes). Future studies are needed to understand the underlying complexity and guide the future interventions.

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The data used for Chapter 3 was provided by Dr. Lorig from the Department of Medicine – Immunology & Rheumatology at Stanford University, Stanford, CA. The data used for Chapter 4 was public-use data from the National Health Interview Survey.

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NOMENCLATURE

CDSMP	Chronic Disease Self-Management Program
CFI	Confirmatory Factor Index
CI	Confidence Interval
CRN	Cost-related Medication Non-adherence
EBP	Evidence-Based Program
ES	Effect Size
ISPOR	International Society for Pharmacoeconomics and Outcome Research
MAM	Multidimensional Adherence Model
MMAS	Morisky Medication Adherence Scale
MPR	Medication Possession Ratio
NCHS	National Center for Health Statistics
NHIS	National Health Interview Survey
PHQ	Patient Health Questionnaire
PPR	Patient-Provider Relationship
RMSEA	Root Mean Square Error of Approximation
SE	Standard Error of the Effect Size
SEM	Structural Equation Modeling
SMI	Serious Mental Illness
SRMR	Standardized Root Mean Square Residual

w	Inverse Variance Weight of the Effect Size
WHO	World Health Organization

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1. INTRODUCTION

1.1. Background

Over the past decades, increased use of pharmacotherapy or medication treatment was observed in the US [1]. About 90% of older Americans are on at least one prescription medication, and more than one-third of older adults are on polypharmacy (i.e., five or more prescription medication) [2]. The cost of prescription medication reached $265 billion in 2013 [3], and the cost of prescription medication is expected to rise even further in the next decades with the growing size of an older adult population [4].

Assuming evidence-based prescription is practiced by prescribers, prescription medication can only be as effective as it is administered as prescribed. Poor medication adherence is associated with treatment ineffectiveness, adverse health outcomes, increased healthcare costs, and even death [5, 6]. For instance, poor adherence to adjuvant hormonal medication (e.g., tamoxifen) was associated with shorter recurrence periods, loss of life years, increased medical costs, and worse quality of life in female breast cancer patients [7]. Recent studies support the notion that improved medication adherence significantly lowers healthcare costs [8, 9].

Given the context, poor medication adherence has been a persistent public health challenge. Based on the quantitative review of 328 studies, DiMatteo reported that one-in-five patients did not adhere to his or her prescription medication [10]. With the expectation that the rates of medication non-adherence would be underestimated in clinical trials due to the attention received by the patients, Osterberg and Blaschke [11] reported medication adherence rates of 43 to 78% (or medication non-adherence rates of 22 to 57%). Based on a more recent review [12], the rate of medication non-adherence has remained problematic (43%).

Past research in the area has expanded our understanding of factors influencing medication adherence (e.g., patient-provider relationship) and identified potential leveraging points for improving medication adherence. However, what we know and how we intervene in this persistent public health issue can be further improved via additional research. For example, while patient-provider relationship has been suggested as an influencer of medication adherence, there is a limited understanding about how different components of the relationship or types of medical interaction influence medication adherence. Therefore, this dissertation aims at investigating the modifiable factors that may drive medication adherence and thereby inform interventions for promoting medication adherence in older adults. The core components of this dissertation are three separate researches that involve investigation of the association between medication adherence and different modifiable factors.

Before delving deeper into the dissertation research, this section provides the background by providing a brief overview of how medication adherence is defined and measured, as well as its theoretical underpinning.

1.2. Definition of Medication Adherence

The World Health Organization (WHO) [13] defines adherence as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider" (p.17). The International Society for Pharmacoeconomics and Outcome Research (ISPOR) [14] provides a more detailed definition: "the extent to which a patient acts in accordance with the prescribed interval and dose of and dosing regimen." The two definitions share the common idea that medication adherence refers to the degree to which a patient's behavior conforms with the prescription instruction. The ISPOR's definition provides a more specific criteria of medication adherence, but the definition may imply a passive role of a patient in a healthcare setting. On the other hand, the WHO's definition, by using the term 'agreed recommendation,' highlights the active role of patients in their healthcare.

In the past literature, adherence has also been used synonymously with compliance and persistence. For example, Vrijens *et al.* [15] included initiation, implementation, and discontinuation as components of adherence behavior. However, the ISPOR distinguishes *persistence* from adherence, such that *persistence* is defined as the duration of time since the treatment initiation to the discontinuation. The lack of standardized definitions results in inconsistencies and difficulties in summing or comparing outcomes from different studies [16]. In research practices, the difficulties in differentiating the terms is partly associated with the difficulties in operationally distinguishing those terms.

1.3. Operational Definition of Medication Adherence

Operationally, medication adherence can be defined in a variety of ways. Direct observation by caregivers or healthcare providers is one of many ways to measure medication adherence. Direct observation allows collecting multiple aspects of medication adherence (e.g., timing, dosages, and frequencies), but the direct approach is not always feasible for outpatients and can be costly. Potential bias with the measurement can be induced from patients' desire to be viewed favorably by the researchers, caregivers, and healthcare providers [17-20].

Alternatively, patients can be asked to self-report medication adherence behaviors via interview or standardized questionnaires (e.g., Morisky medication adherence scale (MMAS) [21]). Sometimes, physicians can be asked about how well their patients conform with the prescription. More objective measures include pill counts, secondary data approach, biochemical assessment, and electronic monitoring. Pill counts refers to counting remaining number of pills. Medication Possession Ratio (MPR) is one of the most commonly-reported secondary data approach. Using the existing electronic health records, MPR estimates the proportion of total days covered by the medication over the number of days between the first and last refill. Pill counts or a secondary data approach may be accompanied by the billing information or insurance claims for more accurate information. Biochemical assessment (e.g., urine or blood analysis) assesses the presence of and amount of biochemical substances and cells that indicate intake of the medication. An example of electronic monitoring is medication event monitoring system, which records the date and time a medication container was opened.

Despite the presence of multiple modes of measuring medication adherence, there is no “gold standard.” These methods only provide proxy measures of medication adherence. Even the direct observation method may not be able to catch patients hiding medication under their tongue. Both pill counts and medication event monitoring system are based on the assumption that missing pills or opening containers indicate the amount of medications consumed or frequency of medication consumption by the patients. Biochemical assessment outcome could depend on the individual’s metabolism rate and the types of medication. Each measurement approach has benefits and drawbacks, and it is recommended to use multiple approaches for a more accurate measure of medication adherence [13, 22].

1.4. Conceptual Framework

According to Leventhal and Cameron [23], there are five categories of theoretical perspectives to examine medication adherence: biomedical, behavioral (operant and social learning), communication, cognitive (rational decision), and self-regulatory theories. The biomedical perspectives view patients as passive recipients of healthcare and focus on dispositional characteristics (e.g., demographic and personality characteristics) of patients rather than contextual or cognitive factors. The behavioral models incorporate internal and external cues to the adherence behavior, behavioral patterns, and habituation. An example of the behavioral models is Bandura’s Social

Learning Theory [24]. The communications perspective, as its name implies, focuses on communication to patients about adherence and focuses on development and delivery of message and receipt, comprehension, and acceptance of the message. The rational belief models view rational thought-process (e.g., patients' perceived benefits and barriers of engaging the behavior) as the key determinant of the behavior. An example of a rational belief model is the Health Belief Model [25]. The self-regulatory models view patients as active decision-makers about their adherence behavior. The self-regulatory models typically incorporate three stages: the cognitive representation of health threat, plan of action, and appraisal or coping. Unlike behavioral or rational belief models, the self-regulatory models incorporate the potential influence of emotional reactions at all three stages. While all five categories of theories add value to understanding and predicting medication adherence, these traditional theories tend to focus on one or two dimensions of the known risk factors.

A general consensus is that medication non-adherence is derived by the interplay of multitudes of factors, beyond just intrapersonal or interpersonal factors as described in many traditional models. The WHO's multidimensional adherence model (MAM) was developed based on years of empirical research evidence [13]. The WHO's MAM describes five categories of factors that drive treatment adherence in long-term conditions. The five categories are patient-related factors (e.g., age, gender, attitudes, and knowledge), health condition-related factors (e.g., symptom severity and depression), treatment-related factors (e.g., complexity, treatment duration, and treatment cost), healthcare system-related factors (e.g., patient-provider relationship), and socioeconomic factors (e.g., education, ethnicity, social support, and financial status) [21]. Unlike the traditional behavioral health models, the WHO's MAM includes factors that are beyond the individual-level factors, and it somewhat reflects the shift in the public health perspective away from victim (patient)-blaming and towards a systems perspective. Within the systems perspective, patients are structurally and functionally related to other parts of the system (e.g., healthcare providers). Wu *et al.* [26] used the MAM to determine whether the five dimensions of factors would predict medication adherence among patients with heart failure. The study finding supported some of the factors, but not all of the factors in the MAM were associated with medication adherence at 3- and 6-month follow-up assessments in their study population (Wu *et al*., 2008). One plausible explanation for the observation may be related to the fact that the MAM is not conceptualized specifically for medication adherence, but for general treatment adherence [26]. Also, one major weakness of the MAM is that the model does not explain how different categories of factors interact or influence adherence behavior.

There have been attempts to combine traditional models (or at least constructs of the traditional models) with empirical evidence. Piette *et al.* [27] proposed a conceptual framework that describes the effects of patient-, medication-, healthcare providers-, and healthcare systems-related factors on the relationship between patients' adherence to their medication and out-of-pocket cost related to their medication. Unlike the MAM, Piette's model explains how different drivers influence a patient's medication adherence behavior. This dissertation did not utilize Piette's model, because the conceptual framework was specific to cost-related medication non-adherence.

Instead, this dissertation utilized a conceptual framework that was described by McHorney [28]. Named as the Proximal-Distal Continuum of Adherence Driver Model, the conceptual framework maps the drivers of medication adherence along an etiological continuum of impact-strengths based on empirical evidence. Based on empirical evidence, the prepositions for the McHorney's adherence model were: (1) lack of communication between patients and physicians about medication adherence status; (2) medication non-adherence not being driven by personality or demographic characteristic; (3) patients' information needs not always being met; (4) inconsistency in healthcare providers' communication about prescription medication; and (5) medication non-adherence being a rational behavior that is based on a decision-making process. Given these prepositions, it was also hypothesized that patients hold different beliefs and attitudes about different medications and, hence, may adhere differently to different medication.

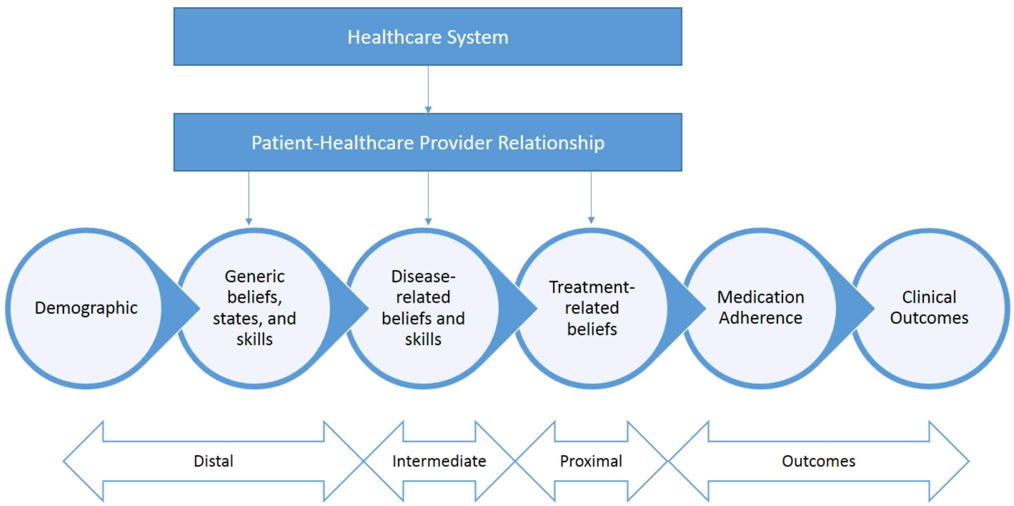
According to the Proximal-Distal Continuum of Adherence Driver Model, the treatment-related beliefs and skills are the strongest drivers (i.e., proximal drivers) of medication non-adherence followed by the disease-related beliefs and skills (i.e., intermediate drivers), generic beliefs, health states, and skills (i.e., distal drivers), and sociodemographic characteristics (i.e., distal drivers) [28, 29]. The proximal drivers of medication adherence include perceived need for medications, perceived medication concerns, and perceived medication affordability. Although it is not depicted in the model, McHorney hypothesized that perceived need for medications and perceived medication concerns are stronger drivers than perceived medication affordability [28].

Under the Proximal-Distal Continuum of Adherence Driver Model, proximal drivers are influenced largely by intermediate drivers, and intermediate drivers are largely influenced by distal drivers. Examples of intermediate drivers include patients' knowledge of their condition and treatment, beliefs and attitudes about side effects, health information-seeking behavior, trust in their healthcare providers, and participation in their care. Examples of distal drivers are demographic characteristics, as well as physical and mental health status, self-efficacy, and social support.

The Proximal-Distal Continuum of Adherence Drivers Model overcomes the caveats of the traditional behavioral theories by combining the constructs from the traditional behavioral theories (e.g., necessity-concerns framework and Brenner's proximal-distal continuum) and empirical evidence [28]. By assuming the linear relationship between the drivers, the model can suggest simpler models for analyses, but its ability to depict the real relationship between drivers (e.g., moderation or feedback loop) is limited. Furthermore, the model focuses heavily on patient-level factors.

In this dissertation, an extended Proximal-Distal Conitnuum of Adherence Drivers Model was proposed (Figure 1). The extended model includes patient-provider relationships and healthcare system to depict the effects of these factors on medication adherence. In the extended model, it was hypothesized that patient-provider relationship can influence the generic, disease-related, and treatment-related knowledge, attitudes, and skills. The healthcare system can influence patient-provider relationship by influencing the training of healthcare providers or the potential of changing appointment schedules. The extended model should provide a more holistic perspective of the medication non-adherence than the original model.

Figure 1. Extended Proximal-Distal Continuum of Adherence Drivers Model



1.5. Structure of Dissertation

The remaining portion of this dissertation will describe three research papers that examine different factors associated with medication adherence in older adults using the extended Proximal-Distal Conitnuum of Adherence Drivers Model.

The first paper used a systematic literature review and meta-analysis to describe the prevalence of medication non-adherence and overview the association between patient-provider relationship and medication non-adherence among community-dwelling older adults. To date, there is no review in the topic that specifically focuses on the older population. Also, there is limited knowledge of how different aspects of patient-provider relationship or medical interaction are related to patients' medication adherence. The first research paper attempted to fill the knowledge gap and add to existing knowledge by highlighting the current state of research. Understanding the differential effects of patient-provider relationship on medication adherence in the population will provide valuable evidence for program and policy developers to enhance the design of interventions.

The second paper used multiple linear mixed-effects models to examine the long-term impacts of the Chronic Disease Self-Management Program (CDSMP) on medication non-adherence in older adults. While CDSMP has shown to improve medication adherence in 12 months, there is inadequate evidence about how CDSMP influences medication adherence. The second research paper attempted to fill the knowledge gap by examining the relationship between long-term program impacts on medication adherence and different aspects of short-term program impacts (e.g., self-rated health, depression, and communication with doctors).

The third paper used structural equation modeling to examine the causal paths between poverty, patient attitudes, and cost-related medication non-adherence (CRN). Extant evidence indicates that CRN is influenced by both financial and non-financial factors. However, there is a limited understanding about how effects of financial factors on CRN may be further augmented or diminished by nonfinancial factors, such as patient satisfaction and perceived access to care. By exploring the modifiable, non-financial factors, the study findings can inform public health and clinical practitioners about a potential intervention point to improve medication adherence, especially among those with a greater financial burden.

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2. MEDICATION ADHERENCE AND PATIENT-PROVIDER RELATIONSHIP AMONG COMMUNITY-DWELLING OLDER ADULTS: SYSTEMATIC LITERATURE REVIEW

2.1. Overview

Background: Medication non-adherence is a public health problem that is related to various health-related outcomes and treatment inefficiency in patients. While patient-provider relationship (PPR) is known to be associated with medication adherence, the magnitudes and directions of the association between different aspects of PPR and medication adherence are understudied.

Objective: To describe the prevalence of medication non-adherence and overview the association between different aspects of PPR and medication adherence among community-dwelling older adults.

Methods: Systematic search of literature from major databases with the key words, such as medication adherence and patient-provider relationship yielded 2,148 articles. Of the articles retrieved from the literature search, 10 articles were included in this review.

Results: Using a fixed-effects model, the mean prevalence rate of medication adherence was 67% (SE = 0.31; 95% CI = [66.53%, 67.75%]). The most frequently measured aspect of PPR was the instrumental dimension (i.e., task-oriented). A quantitative summary of the association between PPR and medication adherence was not

feasible due to the diversity of PPR definitions and measurements. Of the instrumental dimensions examined, information exchange was positively associated with medication adherence, but discussion about barriers was negatively associated with medication adherence.

Conclusions: There is a high prevalence of medication non-adherence among community-dwelling older adults. Limited evidence suggests promoting effective information exchange between patients and providers can help attenuate the problem. More rigorous, longitudinal studies that use better measurements are needed to expand our understanding of the relationship between PPR and medication adherence.

2.2. Introduction

Patient-provider relationship (PPR) is one of the key drivers of medication adherence [1-3]. In a meta-analysis, Haskard-Zolnierek and Dimatteo [4] found a strong positive relationship between physicians' communication and patients' adherence to treatments. By examining the effects of physician communication interventions on patients' treatment adherence, the meta-analysis suggested a potential causal link between the physicians' communication and patients' treatment adherence [4]. Other studies suggested positive associations between PPR and health literacy [5, 6], treatment-related attitudes [7], and patient satisfaction [8].

While the past research has suggested the positive relationship between better PPR and optimal treatment adherence [4], the evidence was still limited, and thus the causal effect was inconclusive. One of the reasons for the inconclusiveness is the complexity in defining and measuring PPR. PPR describes a state of being connected, as well as the process of connecting patients and healthcare providers, which involves interactions of the two systems [9]. Ong *et al.* [10] described medical interactions in terms of purposes of medical interaction, types of interaction analysis models, and types of medical communication behaviors. According to Ong *et al.* [10], Medical interactions serve three purposes: to create a good interpersonal relationship, to exchange information, and to make medical decisions [10]. There are several approaches to analyze medical interactions, and the approaches can be described in terms of what they measure, clinical relevance, observational strategies, reliability and validity, and channels of communicative behaviors that it measures [10].

The interaction activities between patients and healthcare providers can be categorized into affective or instrumental behaviors, verbal or non-verbal behaviors, and high- or low-controlling behaviors [10]. The affective behavior type involves emotions, trust, respect, and empathy. On the other hand, the instrumental behavior type incorporates task-oriented behaviors, such as giving and seeking information and making treatment-related decision. Ong *et al.* [10] linked affective behavior type to the 'care' system, which reflects 'patients' need to feel known and understood,' and instrumental behaviors to the 'cure' system, which reflects 'patients' need to know and understand.'

The high- or low-controlling behaviors are reflection of the power distribution between patients and their healthcare providers. The traditional PPR model is the paternalistic model, in which healthcare providers tend to lead the interactions and patients are appeared as recipients of care. More recent PPR models include patientcentered and shared-decision models, in which healthcare providers tend to show less controlling-behaviors and patients are appeared as partners or collaborators. Patients who worked in a partnership with their physicians were more likely be satisfied than the patients who engaged in the paternalistic relationship [11]. Past studies have also shown positive effects of the collaborative PPR in treatment adherence [12-14].

Understanding effects of the different aspects of PPR on medication adherence will enable the formulation of effective and efficient medical interaction strategies for improving medication adherence. Barlett *et al.* [15] suggested that magnitude of the correlation between affective behaviors and medication adherence (r=0.19) was greater than magnitude of the correlation between instrumental behaviors and medication adherence (r=0.03). The Barlett's study implies a stronger relationship between affective interaction behaviors and treatment adherence in relative to the relationship between instrumental interaction behaviors and treatment adherence [15]. The past reviews related to the topic included diverse populations and broad medical treatments [4] and did not focus on older adults. There is a need for an overview of the empirical evidence to determine direction, size, and significance of the relationship between different components of medical interactions and medication adherence.

The objectives of this systematic literature review are two folds. First, the review summarized the prevalence of medication non-adherence among community-dwelling older adults. Second, the review attempted to provide an overview of the association between the different aspects of PPR and medication adherence among community-dwelling older adults in an outpatient setting. In this review, community-dwelling older adults refer to older adults who live independently in a community and are not institutionalized.

2.3. Methods

2.3.1. Definitions

For this literature review, *medication adherence* was defined as the extent to which an individual takes his or her medication as prescribed by a healthcare provider. The meta-analysis used a relatively-general definition to ensure inclusion of more studies as long as the studies examined at least one aspect of medication adherence (e.g., type of medication adherence or degree of medication adherence). Furthermore, the studies were not excluded from the current review based on the measurement types. Operational definitions for medication adherence included self-reported measures, Medication Possession Ratio (MPR), pill counts, biochemical assessment, and electronic monitors. Good medication adherence is typically defined as at least 80% of MPR or not missing any dose during an observed period of time. *Provider-patient relation* (PPR) was defined as the instrumental or affective interactions. Examples of the instrumental interactions included decision-making and information exchange. Examples of the affective interactions included trust and feeling of being understood. PPR can be measured from provider's and/or patient's perspectives surveys or from a third-person's observation.

2.3.2.Literature Search

The literature search was conducted in three electronic databases: PsycInfo, Medline (Pubmed), and Scopus with Boolean connections using the key words, such as *prescription, adherence or compliance, and patient physician relationship, interaction, communication, shared decision making, or trust*. The search terms were determined through a preliminary literature search, consultation with a librarian, and a discussion among the authors (SL, MO, DD, AH, and LJ). As a complimentary search strategy, the primary reviewer (SL) conducted reference searches of the identified articles to identify additional papers.

2.3.3.Literature Selection

Each identified paper was screened for its relevance based on a set of pre-determined inclusion and exclusion criteria. Papers were included if the papers were: (1) written in English; (2) having at least one quantitative result; (3) examining the association between PPR and medication adherence; and (4) published in 2007 or after (no more literature was searched after July 22nd, 2017). Studies were excluded if any of the following exclusion criteria was met: (1) focusing on population younger than 50 years old; (2) not focusing on provider-prescribed medications; (3) not focusing on self-administered medications; (4) not focusing on oral medications (e.g., eye drop and inhaler); (5) focusing on short-term conditions; (6) focusing on populations with or medications for cognitive limitations, psychiatric symptoms, or substance abuse; (7)

focusing on communicable diseases; (8) focusing on institutionalized population; or (8) theoretical research, literature reviews, or utilizing only qualitative research methods.

The screening was performed on the papers' titles, abstracts, and then on their full texts. Two reviewers (SL and AY) independently scanned the randomly-selected 10% of the papers generated by the search based on the inclusion and exclusion criteria. If the titles did not provide sufficient information to decide the inclusion status, the papers' abstracts were scanned. Similarly, if the abstracts did not provide sufficient information to decide the inclusion status, the papers' full texts were scanned. The two reviewers compared their decisions about the inclusion status of the scanned papers and reached consensus. In the next step, the primary reviewer (SL) screened all remaining identified papers.

2.3.4.Quality Assessment

A quality assessment checklist was constructed based on the National Heart, Lung, and Blood Institute's quality assessment tool for observational cohort and cross-sectional studies [16], Effective Public Health Practice Project tools [17], and Critical Appraisal Skills Programme tools [18]. The two reviewers (SL and AY) independently reviewed the quality of the selected papers using the constructed quality assessment checklist. The two reviewers compared their quality assessment decisions and reached a consensus. Most of the selected studies included only a single cohort, and hence the item number 8 (i.e., if there was more than one cohort, were all the subjects selected or recruited from the same or similar populations (including the same time period)?) was not applicable. Thereby, the mean of the twenty remaining items were used as the overall quality score.

Table 1. Quality assessment checklist

No	Criteria	Scoring
1	Was the research question or objective in this paper clearly stated?	Yes = 1, No or Not Reported = 0
2	Was the study population clearly specified and defined? (Demographics)	Yes = 1, No or Not Reported = 0
3	Was the study population clearly specified and defined? (Location)	Yes = 1, No or Not Reported = 0
4	Was the study population clearly specified and defined? (Time period)	Yes = 1, No or Not Reported = 0
5	Were the individuals selected to participate in the study likely to be representative of the target population?	Yes = 1, No or Not Reported = 0
6	Was there any significant difference between those who participated in the study and those who did not participate in the study?	Yes or Not Reported = 0, No = 1
7	Was the participation rate of eligible persons at least 50%? (% of those who participated from total number of reached for recruitment)	Yes = 1, No or Not Reported = 0
8	If there were more than one cohort, were all the subjects selected or recruited from the same or similar populations (including the same time period)?	Yes = 1, No or Not Reported = 0
9	Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes = 1, No or Not Reported = 0
10	Was a sample size justification, power description, variance, or effect estimates provided?	Yes = 1, No or Not Reported = 0
11	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes = 1, No or Not Reported = 0
12	Were measure(s) of PPR clearly defined?	Yes = 1, No or Not Reported = 0
13	Were the tools or methods used to measure PPR valid?	Yes = 1, No or Not Reported = 0
14	Were the tools or methods used to measure PPR reliable?	Yes = 1, No or Not Reported = 0
15	Were measure(s) of medication adherence clearly defined?	Yes = 1, No or Not Reported = 0
16	Were the tools or methods used to measure medication adherence valid?	Yes = 1, No or Not Reported = 0
17	Were the tools or methods used to measure medication adherence reliable?	Yes = 1, No or Not Reported = 0
18	Were multiple tools or methods used to measure medication adherence?	Yes = 1, No or Not Reported = 0
19	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between PPR and medication adherence?	More than sociodemographic factors = 2, At least

Table 1. (Continued)

No	Criteria	Scoring
	(Key confounding variables included but not limited to: income, out-of-pocket cost, patient beliefs & attitudes, regimen complexity, regimen duration, and depression)	sociodemographic factors = 1, No = 0
20	Were the statistical methods appropriate for the study design?	Yes = 1, No or Not Reported = 0
21	Were the methods for performing the analyses described in sufficient detail?	Yes = 1, No or Not Reported = 0

2.3.5.Data Extraction

From the selected papers, the primary reviewer (SL) extracted the study characteristics (author(s), publication year, data source (e.g., primary or secondary data), study design, location where the study was conducted (e.g., country, state, city, or region), sample sizes, patient demographics, diagnostic characteristics, medication types, medication adherence variable(s), PPR variable(s), forms of data analysis, control variables, and measure of association between medication adherence and PPR). For medication adherence and PPR variables, definition of the measurements, types of measurement tools, levels represented (e.g., dose or intensity), dichotomization of variables, raters (e.g., patient, provider, researcher, or others), means or proportions, and standard deviations or variances were coded. If a study used more than one measure to index the same construct (medication adherence or PPR), each measure was coded separately. Furthermore, if the study reported the data for subsamples that were distinctively different by a characteristic that was commonly found in other studies (e.g., gender), the subsamples were treated as independent studies. However, if the subsamples were different by a characteristic that was not commonly found in other studies (e.g., have or do not have problem with medication cost), the data from the subsamples were pooled (e.g., using Mantel-Hetzel method for odd ratios).

2.3.6.Effect Sizes

The effect size calculation for the current review primarily followed the instruction from the book, *Practical meta*-analysis, by Lipsey and Wilson [19]. The effect size (ES), standard error of the effect size (SE), and the inverse variance weight of the effect size (w) were calculated for each of the commonly-reported participant characteristics (e.g., age, sex, and race). While not all ten selected studies reported race in an identical set of categories, the proportion of Whites could be obtained from the eight studies (80%). Of the eight studies, two studies did not include any Whites in their studies (i.e., proportion of zero). If proportions are less than 0.2 or greater than 0.8, the direct proportion effect size statistics (as used for sex) will overestimate the degree of heterogeneity and do not produce a reliable ES [19]. Thereby, the ES for race was estimated in logits and then was converted back to proportions for interpretations. The mean effect sizes for age, sex, and race were estimated by weighting the ES from each study by the w from the corresponding study. Other sociodegmographics (e.g., education and income) were not reported in comparable formats to calculate mean effect sizes.

Most studies used either binary or dichotomized measure medication adherence. Hence, direct proportion effect size statistics was used as the ES. Under the assumption that the measures of medication adherence were comparable, heterogeneity of the ES across the studies in terms of population characteristics or study country was examined using the Q-statistics (fixed-effects model).

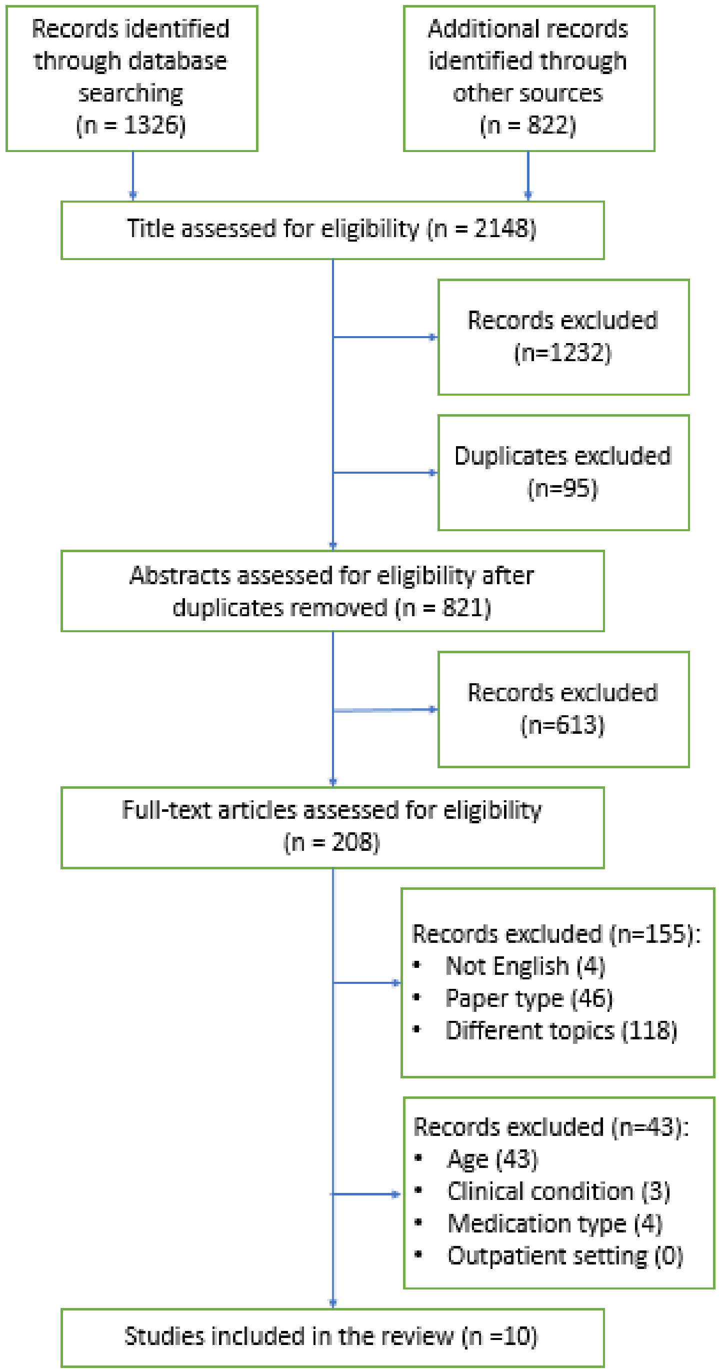
The measures of PPR varied significantly, and hence a summary or comparison across the reported measures of PPR was not feasible. Similarly, a summary or comparison of the association between medication adherence and PPR was not feasible due to the heterogeneity of the reported measures. Thereby, the descriptives of what constructs were measured, in what frequencies, and direction of the association (e.g., positive, negative, no difference, and unknown) were documented. All the procedures were performed using the Microsoft Excel and R.

2.4. Results

2.4.1. Study Characteristics

Ten papers [20-29] were included in this review. The flow chart of the literature selection process was depicted in Figure 2 [30]. Detailed description of the ten selected studies were provided in Table A1 (Appendix A). All ten studies were cross-sectional studies, and eight out of the ten studies [21-26, 28, 29] were based on primary data. The selected studies were conducted at multiple geographic locations, including the US (70%) [20-24, 27, 29], Philippines (10%) [26], Brazil (10%) [25], and Republic of Korea (10%) [28] (Table A1). Of the ten studies, four focused on hypertension (40%) [21, 24, 27, 29], one focused on diabetes (10%) [20], and other studies did not focus on any specific chronic conditions (50%) [22, 23, 25, 26, 28]. while one study (10%) failed to specify the provider type [27], other studies looked at patients' relationship or interaction with doctors or physicians (70%) [20-23, 25, 26, 29], pharmacists (10%) [28], or multiple provider types (e.g., doctors or nurses) (10%) [24].

Figure 2. Flow chart of literature selection process



The quality assessment score of the included studies ranged from 0.60 to 0.81 (the quality assessment score ranged from 0 to 1, with a higher score indicating the better quality). A few methodological issues were identified (Table 2). All of the studies were based on the cross-sectional data, hence causality cannot be drawn from the study-design or the data. Furthermore, all the studies either failed to report or reported statistically-significant differences between those who participated in the study and those who did not participate in the study. Only one of the included study provided sample size justification, power, variance, or effect estimate [27]. Most of the included studies (70%) used binary variables to report PPR and medication adherence [21-27]. Furthermore, none of the included studies used multiple methods to measure medication adherence. All the included studies used patients' self-reported data for measuring medication adherence. Eight studies (80%) performed multivariate analyses after controlling for sociodemographic variables, as well as condition-, prescription-, or patients' attitudes-related variables [20, 21, 23, 24, 26-29].

Table 2. Quality assessment results (Score ranges from 0 to 1 with a higher score indicating better study quality)

Studies		Heisler *et al*, 2007 [20]	Kressin *et al.*, 2007 [21]	Wilson *et al.*, 2007 [22]	Donohue *et al.*, 2009 [23]	Turner *et al.*, 2009 [24]	Luz *et al.*, 2011 [25]	Guz *et al.*, 2013 [26]	Holt *et al.*, 2013 [27]	Jin *et al.*, 2016 [28]	Lee *et al.*, 2017 [29]
Quality criteria	**1**	1	1	1	1	1	1	1	1	1	1
	2	1	1	1	1	1	1	1	1	1	0
	3	1	1	1	0	1	1	1	1	1	1

Table 2. (Continued)

Studies		Heisler *et al*, 2007 [20]	Kressin *et al.*, 2007 [21]	Wilson *et al.*, 2007 [22]	Donohue *et al.*, 2009 [23]	Turner *et al.*, 2009 [24]	Luz *et al.*, 2011 [25]	Guz *et al.*, 2013 [26]	Holt *et al.*, 2013 [27]	Jin *et al.*, 2016 [28]	Lee *et al.*, 2017 [29]
	4	1	0	1	1	1	1	0	0	0	1
	5	1	0	1	0	1	1	0	0	0	1
	6	0	0	0	0	0	0	0	0	0	0
	7	1	1	1	1	1	1	0	1	1	0
	8	0	1	*	*	*	*	*	*	*	*
	9	1	1	1	1	1	1	1	1	1	1
	10	0	0	0	0	0	0	0	1	0	0
	11	1	0	0	0	0	0	0	0	1	1
	12	1	1	1	1	1	1	1	1	1	1
	13	1	1	0	1	1	0	0	1	0	1
	14	1	0	0	0	0	0	0	0	0	1
	15	1	1	1	1	1	1	1	1	1	1
	16	1	1	1	1	1	1	1	1	1	1
	17	0	0	0	1	0	1	1	0	0	1
	18	0	0	0	0	0	0	0	0	0	0
	19	2	2	0	2	2	0	2	2	2	2
	20	1	1	1	1	1	0	1	1	1	1
	21	1	1	0	0	1	1	1	1	1	1
Quality Score		0.8	0.7	0.6	0.7	0.8	0.6	0.6	0.7	0.7	0.8

2.4.2.Participant Characteristics

The ten selected studies included a total of 25,010 patients (Table 3). Of the ten selected, seven studies [20, 22, 24-28], in which both mean and standard deviation of age were obtainable, were used to estimate the mean age of the total participants. The mean age was 71 years old (standard error [SE]= 0.02; 95% Confidence Interval [CI] = [70.75, 70.83]). The mean proportion of the female was 59% (SE = 0.31; 95% CI = [58.15%, 59.39%]), and the mean proportion of Whites was 82% (95% CI = 81.09%, 82.20%).

Table 3. Summary characteristics of the study participants from the studies included in the review

Studies		Heisler *et al*, 2007 [20]	Kressin *et al.*, 2007 [21]	Wilson *et al.*, 2007 [22]	Donohue *et al.*, 2009 [23]	Turner *et al.*, 2009 [24]	Luz *et al.*, 2011 [25]	Guz *et al.*, 2013 [26]	Holt *et al.*, 2013 [27]	Jin *et al.*, 2016 [28]	Lee *et al.*, 2017 [29]
Sociodemographic Characteristics	**N**	1558	793	17569	1001	202	1017	325	2194	160	191
	Age (Mean (SD))	69 (8.7)	66 (NA)	75 (7.0)	66 (NA)	77 (5.5)	70 (7.8)	70 (0.38) *a*	75 (5.5)	68 (3.9)	70 (NA) *b*
	Primary Race	White (70%)	White (54%)	White (88%)	White (86%)	Black (65%)	White (53%)	Asian (100 %)	*c*	Asian (100 %)	White (60%)
	Female	54%	*d*	59%	50%	66%	66%	62%	59%	70%	78%

a = Mean and standard deviation were estimated based on reported frequency data: 61-70 (62.2%); 71-80 (26.2%); 81-91 (11.7%).
b = less than 65 (18%); 65-75 (49%); $\geq$ 76 (33%). Mean and standard deviation could not be estimated, because the minimum and maximum ages were not specified. Therefore, mid-point of the median category was presented in the table.
c = Proportion of primary race was not specified (African American (31%)).
d = While the frequency or percentage was not provided, the authors indicated in the discussion that "we only studied regular users of the VA (Veterans Affairs) system, … the VA system cares primarily for male patients, so our results may not be generalizable to women…"

2.4.3. Medication Adherence

The reported prevalence of medication adherence ranged from 48% to 86% [20-29]. Under the crude assumption that the different measures were comparable, the mean prevalence rate of medication adherence was 67% (SE = 0.31; 95% CI = [66.53%, 67.75%]). There was a statistically-significant difference in the prevalence rates of medication adherence across the studies (Q = 1535.00, $df = 5$ $p < 0.05$). There was a statistically-significant difference between the US and non-US countries ($Q_b = 29.27$, $df = 1$, $p < 0.05$). The mean prevalence rate of medication adherence was 67% (SE = 0.31; 95% CI = [66.76%, 67.99%]) in the US [20-24, 27, 29] and 55% (SE = 2.25; 95% CI = [50.70%, 59.51%]) in countries other than the US [25, 26, 28].

2.4.4. Patient-provider relationship

Six of the selected studies (60%) measured the instrumental interaction [20-22, 25, 28, 29], one (10%) measured the affective interaction [24], two (20%) measured patients' trust in their physicians [23, 26], and two (20%) measured patients' perception about their PPR in general [25, 28]. Of the six studies that measured the instrumental interactions, two (33%) examined information exchange-related interaction [28, 29] and one (17%) examined both information exchange-related interaction and patients' involvement in decision-making [20]; two (33%) examined discussion of barriers [22] or making adherence easier [21]; and one (17%) examined frequency of patient-physician dialogue about health/treatment [25]. Due to the diversity of the operational definition of PPR, a summary statistic for PPR was not feasible.

2.4.5. Association between Medication Adherence and PPR

All three studies that measured information exchange-related interaction indicated positive relationship between the interaction type and patients' medication adherence [20, 28, 29]. All two studies that measured discussion of barriers or making adherence easier indicated negative relationship between the interaction type and patients' medication adherence [21, 22]. Only one study [24] measured the affective interaction, and the study did not find any meaningful relationship between the interaction type and patients' medication adherence. The two studies about the relationship between trust and medication adherence were not comparable or summable due to the remarkably-distinct measures of medication adherence (e.g., general medication adherence versus cost-related medication adherence) [23, 26]. According to the study by Donohue *et al.*[23], there wasn't any meaningful relationship between trust and cost-related medication adherence. On the other hand, Guz *et al.*[26] observed a significant and strong relationship between patients' trust in their physicians and medication adherence in Philippine.

2.5. Discussion

The current review examined the relationships between medication adherence and PPR for 25,010 patients across ten studies [20-29]. The prevalence of medication adherence was about 67%, and was lower in non-US countries comparing to the US (55% versus 67%). The selected studies examined diverse forms of PPR, and instrumental interaction (e.g., information exchange and decision-making) was most frequently examined form of PPR.

The prevalence of medication adherence reported in the literature varied significantly across the literature. For example, a review of the antihypertension medication non-adherence among patients with treatment-resistant hypertension varied from 3.3% to 86.1% with the average of 31.2% [31]. The pooled medication adherence rate from the review by Durand *et al.*[31] was comparable to the finding from the current review (medication adherence rates of 67%, which is equivalent to medication non-adherence rates of 33%). Furthermore, the current review also indicated that the medication adherence was poorer in non-US countries (i.e., Brazil, Philippine, and Korea). This finding is also consistent with the recent meta-analysis conducted by Abegaz *et al.*[32]. Abegaz *et al.*[32] focused on the prevalence of non-adherence to antihypertensive drugs among adults, and found that the proportion of non-adherence was to higher in the studies conducted in Africa and Asia relative to American and European studies. A potential explanation to the observed finding may be related to cultural difference. For example, use of complementary or alternative medicine may be associated with lower medication adherence in older adults [33].

The current review indicated that while general information exchange had a positive association with medication adherence, discussion with providers about cost-related barriers or how to make the adherence easier had a negative association with medication adherence. A plausible explanation for the observations is the ‘context.’ For example, the discussion with healthcare providers about cost-related barriers might have occurred more frequently among those who had poorer health outcomes, or who were thought to have poorer medication adherence by their healthcare providers. This explanation, furthermore, highlights the limited ability of the extant literature in drawing the causality between medication adherence and PPR. The relationship between PPR and medication adherence may not be linear, but non-linear (e.g., cyclical relationship) and need more complex dynamic systems perspective in future research.

The current review has a few limitations. First, the number of selected studies in the current review was small, and there was too much heterogeneity with regard to the operational definitions to draw a summary or perform a comparison of the association between medication adherence and the different forms of PPR. Second, all studies included in the review used self-reported measure of medication adherence. None of the studies used multiple measures of medication adherence, as recommended in the literature [34, 35]. Third, all studies included in the review measured PPR from the patients' perception. While patients' perceived PPR provides a meaningful insight, it is desirable to examine PPR from the healthcare providers' perceptions, as well as the symmetry between patients' and providers' perceptions about their relationship.

2.6. Summary and Future Implication

The finding from the current review indicates a significant medication non-adherence problem among older adults and highlights the association between medication adherence and PPR. Promoting patients and providers about effective information exchange will produce desirable outcomes associated with improved medication adherence. While the extant literature provides the rich information about the potential association between the two constructs, the evidence is weak. Also, diversity of operational definitions of PPR and medication adherence, which has been a persistent issue in this topic of research, prevent or limits comparison across studies. As recommended by Lam and Fresco [35], future research should balance reliability and practicability of the measures and use multiple measures to index medication adherence. Furthermore, inclusion of the time components in a research design will enhance the study's capability to explain the causality beyond association.

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3. EFFECTS OF CHRONIC DISEASE SELF-MANAGEMENT PROGRAM ON MEDICATION ADHERENCE AMONG OLDER ADULTS

3.1. Overview

Background: Older adults account for almost one-third of all medication prescribed in the US. Of special concern are the high rates of medication non-adherence in this population. Despite many interventions to promote medication adherence, we know little about the process of achieving medicarion adherence in older adults.

Objective: The purpose of this study was to examine the long-term program impacts on medication adherence from participating in the Chronic Disease Self-Management Program (CDSMP).

Methods: Secondary data from the national CDSMP evaluation was used in this study. The secondary data included CDSMP participants' sociodemographic characteristics, as well as their baseline and 6-month and 12-month follow-up assessments on health and health-related indicators, including medication adherence, self-rated health, depression, and patient communication with doctors. This study included those who were 65 years or older, had one or more chronic conditions, and attended at least the first or second session. Linear mixed models were used to analyze the impact of the short-term changes (i.e., 6 months) in self-rated health, depression, and patient communication skills on the long-term changes (i.e., 12 months) in intentional

and unintentional medication non-adherence. The subset analysis was performed among the participants with self-rated major depression at the baseline.

Results: This study included 687 participants. On average, participants were 74.8 years old and had about three chronic conditions. The majority of the participants were females (83.4%). Self-reported medication adherence did not improve significantly at the 6-month follow-up assessment (p=0.5184) but significantly-improved at the 12-month follow-up assessment (p=0.0214). Among those with self-reported major depression at the baseline assessment, the short-term improvements in depression was associated with the decrease in unintentional medication non-adherence (p=0.0021) and the short-term improvements in self-rated health was associated with the increase in intentional medication non-adherence (p=0. 0447) at the 12-month follow-up assessment.

Conclusions: The long-term impact of CDSMP on medication adherence was influenced by the short-term program impacts on depression and self-rated health. However, this mechanism provided only a limited explanation for the observed improvements in medication adherence. Medication non-adherence is a complex problem that is rooted in multiple inter-related factors. Future research are needed to understand the underlying complexity and guide the future interventions.

3.2. Introduction

Prescription medication has been increasingly used in management of chronic diseases, and especially older adults, who experience more chronic diseases than the younger population. Medication use in older adults accounts for almost one-third of all medication prescribed in the US [1]. With the growth of the older adult population, the use of prescription medication and associated costs are expected to rise substantially in the future. Based a national report on health status, the use of one or more prescription drug among older adults had increased from 74% in 1988-1994 to 90% in 2009-2012 [2]. Also, a use of five or more prescription drug among older adults had increased from 14% in 1998-1994 to 39% in 2009-2012 [2]. In 2015, the US spent an estimated $457 billion on prescription medications, accounting for about 17% of the total US healthcare costs [3]. The rise in expenditure on prescription medication is projected to exceed the growth in total healthcare expenditure [3]. Of special concern are the high rates of medication non-adherence in older population (e.g., about 40% being nonadherent based on the CMS data) [4]. Poor medication adherence is associated with treatment ineffectiveness, poorer clinical outcomes, and increased healthcare costs [5-8].

Based on the vigorous reviews of the literature review about the interventions for supporting medication adherence, complex interventions with multiple components had a greater likelihood of improving medication adherence for the patients with one or more long-term conditions [9, 10]. However, even the most successful intervention was not very effective [9, 10]. Furthermore, complexity of the interventions decreases the likelihood of successful translation of the interventions and make it difficult to identify the essential components of the interventions that are keys to the program successes. In addition, there has been a limited understanding about how each intervention component contributes in improving medication adherence. Filling these knowledge gaps is an essential step to design a sustainable intervention for promoting medication adherence in older adults.

This study attempted to expand the knowledge base by delving deeper and examining an intervention, Chronic Disease Self-Management Program (CDSMP), that has already been shown to be successful in improving medication adherence. CDSMP is a general self-management program that has already been successfully implemented among diverse populations in multiple settings. CDSMP is composed of six 2.5-hour sessions and covers a variety of topics, such as problem-solving skills, exercises, proper use of medication, communication skills, nutrition, and how to evaluate new treatment options [11]. CDSMP has been evaluated across 17 states over 6- and 12-month periods [11, 12]. From the baseline to 6-month follow-up, the program participants showed statistically-significant improvements in various health-related indicators (e.g., social/role activities limitation, depression, communication with doctor, self-rated health, pain, fatigue, and other health-related quality of life) [11]. At the 12-month follow-up, the program effects on self-rated health, fatigue, pain, depression, and communication with doctors were sustained [12]. Furthermore, statistically-significant improvements in medication adherence was observed at the 12-month follow-up assessment [12]. While Ory *et al.* [12] theorized that the long-term improvements in medication adherence could have been influenced by the short-term improvement in other health-related measures, the proposition has not been explored previously.

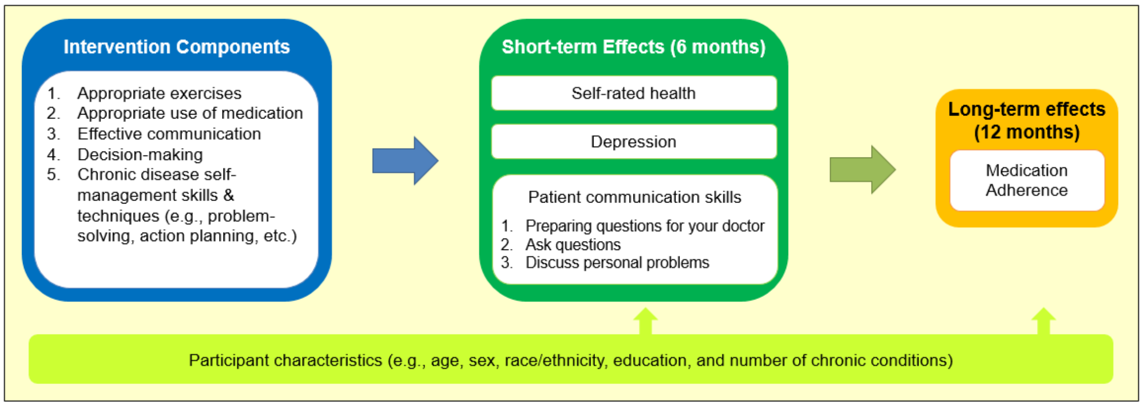
Of the short-term program effects of CDSMP, self-rated health, depression, and communication with doctors are known to be associated with medication non-adherence.

There are strong, consistent evidence for the negative association between medication adherence and depression among diverse populations [13, 14]. For example, the negative association between medication adherence and depression was observed in patients with different chronic diseases, such as arthritis [15], diabetes [16-18], heart disease [19], and hypertension [20]. Thereby, improving depressive symptoms in short-term is expected to improve medication adherence in long-term. Furthermore, previous studies suggested potential moderating effects of baseline depressive symptoms on program impacts on various health-related indicators [21, 22].

Self-rated health was associated with medication non-adherence in many past studies, but evidence has not always been consistent. In a study carried out in China, poor self-rated health was associated with worse medication adherence in patients with hypertension [23], and this result is consistent with the findings from other studies [24-27]. A meta-analysis of 26 studies suggested that the relationship between patient adherence and health status depends on the seriousness of health conditions [28]. Communication with doctors is also acknowledged as an important correlate of medication non-adherence [4]. Thereby, it was hypothesized that the long-term improvements in medication adherence was influenced by the short-term improvements in self-rated health, patient communication, and depression (Figure 3).

With the goal to explore and evaluate the long-term effects of CDSMP on medication adherence, this study examined the potential influence of short-term changes in self-rated health, depression, and patient communication on long-term improvements in medication adherence. Furthermore, a subset investigation was performed among the participants who were at a greater risk of medication non-adherence (i.e., participants with major depression at the baseline measurement).

Figure 3. Conceptual framework that describes the hypothesized process of how CDSMP influences long-term medication adherence



3.3. Methods

3.3.1. Data Source

The secondary data from the national CDSMP evaluation [11, 12] was used for this study. Details of the study design and data collection procedure are available elsewhere [11, 12]. Briefly, the national CDSMP evaluation used a pre-post longitudinal design to assess the effects of CDSMP on various health and health-related indicators. CDSMP workshops were delivered to middle-aged and older adults by 22 organizations in 17 states between August 2010 and April 2011. The data was collected at the baseline and 6- and 12-months from the baseline. The collected data included the participants' sociodemographic characteristics, health, depression, communication with their physicians, medication adherence, and program attendance. All the data used in this study, other than attendance data, was self-reported by the participants using surveys.

3.3.2. Study Participants

The national CDSMP evaluation participant eligibilities were: (1) having at least one self-reported chronic condition, (2) participating in an English or Spanish CDSMP workshop, (3) attending at least the first or second session, (4) participating in a CDSMP workshop for the first time, (4) completing the baseline assessment, and (6) agreeing to participate in CDSMP evaluation. For this study, the study participants were further narrowed down to older adults (i.e., those who self-reported being 65 years old or older at the time of the baseline assessment).

3.3.3. Variables

Medication Adherence. 4-item Morisky Medication Adherence Scale (MMAS-4) (also known as Medication Adherence Questionnaire) was used to measure medication adherence [29]. The MMAS-4 asked the following four items: (1) ever forget to take medicine, (2) ever have problems remembering to take medicine, (3) sometimes stop taking medicine when feel better, and (4) sometimes stop taking medicine when feel worse. Each item was scored “yes” or “no.” Participants who reported an affirmative response to any of the first two items were categorized as “engaging in unintentional medication non-adherence,” and the Cronbach’s alpha for the two-item scale was 0.64. Patients who reported an affirmative response to any of the last two items were categorized as “engaging in intentional medication non-adherence,” and the Cronbach’s alpha for the two-item scale was 0.61. The average score of the four items was used as an indicator for the degree of medication adherence overall. The reliability of the MMAS-4, measured using the Cronbach’s alpha, was 0.56, and is similar to other studies [29, 30]

Self-rated Health. A single item was used to examine the self-rated health: “in general, would you say that your health is excellent, very good, good, fair, or poor?” The response to the item ranged from “excellent” (=1) to “poor” (=5), with a lower score indicating better health. It is a standardized item used in multiple national surveys (e.g., National Health Interview Survey and Behavioral Risk Factor Surveillance System).

Depression. The 8-item Patient Health Questionnaire (PHQ-8) was used as a measure of depression [31]. The PHQ-8 asked how often during the past 2 weeks the participants were bothered by: (1) little interest or pleasure in doing things; (2) feeling down, depressed, or hopeless; (3) trouble falling or staying asleep, or sleeping too much; (4) feeling tired; (5) poor appetite or overeating; (6) feeling bad bout self; (7) trouble concentrating on things; (8) moving or speaking slowly or being very fidgety or restless. Each item was scored “not at all” (=0), “several days” (=1), “more than half the days” (=2), or “nearly every day” (=3). The sum of the eight items were used as the composite score (ranging from 0 to 24, with a higher score indicating severer depression). A score of 10 or higher was considered major depression [31]. The reliability of the scale, among this study population was 0.81, measured using the Cronbach’s alpha.

Communication with Doctors. The following three items were used to assess what the participants do during their visits to their doctors: how often do you (1) prepare questions to ask; (2) ask questions; and (3) discuss personal problems. Each item was scored from "never" (=1) to "always" (=6). Mean of the three items was used as the composite score (ranging from 1 to 6, with a higher score indicating better communication with doctors) [32]. The Cronbach's alpha, among this study population, was 0.78.

Covariates. Participant's self-reported information on age (years), sex, race/ethnicity, years of education (ranging from 1 to 23 years), number of sessions attended (ranging from 1 to 6), and number of chronic diseases were used in this study. Age was calculated by deducting the date of birth from the date of assessment. Participants were asked whether they were diagnosed with the following chronic diseases: Type 1 Diabetes, Type 2 Diabetes, asthma, chronic obstructive pulmonary disease (COPD), chronic lung diseases other than COPD, hypertension, heart disease, arthritis, cancer, depression, anxiety or other mental health condition, or any other chronic condition. The number of sessions attended were calculated by summing the total number of attended sessions out of the six available sessions. The number of chronic conditions was calculated by counting the affirmative responses to each self-reported chronic condition.

3.3.4. Analysis

The baseline characteristics of the study participants were described using mean and standard deviation for interval variables and frequency and percentage for categorical variables. Independent group comparisons (e.g., χ^2 test for categorical variables and two-sample t-test for continuous variables) were used to compare the baseline characteristics of the participants with and without the 6- and 12-month follow-up assessments.

Next, multiple linear mixed models were performed to examine the changes in medication adherence over time (using SAS PROC MIXED and SAS PROC GENMOD). The first set of models were performed to examine the changes in medication adherences, self-rated health, depression, and patient communication from the baseline to 6- and 12-month follow-up assessments controlling for the covariates. The second set of models were performed to examine the changes in medication adherences from the baseline to 6- and 12-month follow-up assessments based on the baseline self-rated health, depression, or communication with doctors after controlling for the covariates. The last set of models were performed to examine the changes in medication adherence from the 6- to 12-month follow-up assessments based on the changes in self-rated health, depression, or communication with doctors from the baseline to the 6-month follow-up assessment after controlling for the covariates. The last sets of models were performed among the overall study population, as well as among the study population with major depression at the baseline assessment.

3.3.5. Institutional Review Board

The secondary analysis of the data was approved by the Texas A&M University Institutional Review Board (IRB).

3.4. Results

3.4.1. Sample Characteristics

This study included 687 participants who completed at least the baseline assessment. Table 4 shows the baseline characteristics of the study participants. In average, age of the study participants was 74.8 years old, years of education was 13, and number of chronic conditions was 2.9. The majority of the study participants was female (83.6%), non-Hispanic (82.8%), and White (60.6%) and attended at least 4 out of 6 CDSMP workshop sessions (80.8%). At the baseline assessment, 18.1% of the study participants reported intentional medication non-adherence, and 38.0% reported unintentional medication non-adherence.

Table 4 also shows the comparison between those who had the complete data and those who did not participate in the 6- or 12-month follow-up assessments. Of the 687 study participants, 572 (83.3%) completed the 6-month follow-up assessment, and 512 (74.5%) completed the 12-month follow-up assessment. Compared to the participants who did not complete the 6-month follow-up assessment, those who completed the 6-month follow-up assessment were more likely to be Whites, had higher workshop completion rates, and reported more chronic conditions, better self-rated health, better depressive symptoms, and better communication with doctors. Similarly, compared to the participants who did not complete the 12-month follow-up assessment, those who completed the 12-month follow-up assessment had higher workshop completion rates and reported better self-rated health and better depressive symptoms.

Table 4. Characteristics of the study participants by follow-up assessment completion status

		6-month assessments			**12-month assessments**		
	Total (n=687)	**Completed (n=572)**	**Not Completed (n=115)**		**Completed (n=512)**	**Not Completed (n=175)**	
	Mean (SD) or Freq (%)	**Mean (SD) or Freq (%)**	**Mean (SD) or Freq (%)**	***p*-value**	**Mean (SD) or Freq (%)**	**Mean (SD) or Freq (%)**	***p*-value**
Age (years)	74.8 (6.84)	74.9 (6.83)	74.3 (6.90)	0.35	74.7 (6.77)	75.2 (7.06)	0.36
Female	574 (83.6%)	476 (83.2%)	98 (85.2%)	0.60	426 (82.6%)	151 (86.3%)	0.26
Non-Hispanic	563 (82.8%)	470 (82.8%)	93 (83.0%)	0.94	423 (83.3%)	140 (81.4%)	0.57
White	416 (60.6%)	359 (62.8%)	57 (49.6%)	<0.01*	315 (61.5%)	101 (57.7%)	0.84
Education (years)	13.0 (3.73)	13.0 (3.76)	12.8 (3.59)	0.72	13.0 (3.73)	12.8 (3.75)	0.51
Number of chronic conditions	2.9 (1.59)	3.0 (1.58)	2.6 (1.59)	0.02*	3.0 (1.53)	2.9 (1.75)	0.57
Workshop completion[a]	555 (80.8%)	488 (85.3%)	67 (58.3%)	<0.01*	434 (84.8%)	121 (69.1%)	<0.01*
Self-rated health	3.1 (0.90)	3.0 (0.90)	3.2 (0.86)	0.03*	3.0 (0.89)	3.2 (0.91)	0.03*
PHQ-8	5.3 (4.62)	5.1 (4.52)	6.3 (5.02)	0.01*	5.0 (4.42)	6.2 (5.08)	<0.01*
Communication with doctors	2.7 (1.36)	2.7 (1.34)	2.3 (1.39)	<0.01*	2.7 (1.37)	2.5 (1.34)	0.25
MMAS-4	0.2 (0.26)	0.2 (0.26)	0.2 (0.26)	0.73	0.2 (0.25)	0.2 (0.26)	0.62
Intentional medication non-adherence	124 (18.1%)	100 (17.5%)	24 (21.2%)	0.34	95 (18.6%)	29 (16.7%)	0.57
Unintentional medication non-adherence	261 (38.0%)	218 (38.1%)	43 (37.4%)	0.88	199 (38.9%)	62 (35.4%)	0.42

SD = standard deviation
* Statistically-significant at alpha = 0.05.
a. Attending at least 4 out of 6 CDSMP workshop sessions

3.4.2. Changes from Baseline to 6- and 12-month Follow-up Assessments

Statistically-significant improvements in medication adherence was observed from the baseline to 12-month follow-up assessment, but not at the 6-month follow-up assessment (Table 5). The odds of engaging in unintentional medication non-adherence reduced significantly from the baseline to the 12-month follow-up assessment, but not at the 6-month follow-up assessment. Table 5 also shows the changes or ratios between the baseline to the 6- and 12-month follow-up assessments for self-rated health, PHQ-8, and patient communication. Compared to the baseline, the odds of reporting poorer self-rated health was lower at both 6- and 12-month follow-up assessments. Similarly, both PHQ-8 and patient communication showed significant improvements from the baseline to the 6- and 12-month follow-up assessments.

Table 5. Adjusted changes or ratio between baseline and follow-up medication adherence

Health-related outcomes	Baseline (n=687)	6-month (n=572)	12-month (n=512)	Baseline to 6-month		Baseline to 12-month	
	Mean (SD) or Freq (%)	Mean (SD) or Freq (%)	Mean (SD) or Freq (%)	Adjusted changes or ratio[a]	*p*-value[a]	Adjusted changes or ratio[a]	*p*-value[a]
Self-rated health	3.06 (0.8966)	2.96 (0.8737)	2.95 (0.9118)	0.78	0.0007*	0.77	0.0028*
PHQ-8	5.31 (4.6241)	4.49 (4.3191)	4.20 (4.3181)	-0.74	<0.0001*	-0.97	<0.0001*
Patient communication	2.65 (1.3591)	2.86 (1.4146)	2.89 (1.4212)	0.16	0.0019*	0.21	<0.0001*
Intentional medication non-adherence	124 (18.1%)	102 (17.9%)	86 (16.8%)	0.98	0.8904	0.92	0.5183
Unintentional medication non-adherence	261 (38.0%)	200 (35.0%)	163 (31.8%)	0.88	0.1667	0.76	0.0057*
MMAS-4	0.20 (0.2559)	0.19 (0.2607)	0.17 (0.2461)	0.01	0.5184	0.02	0.0214*

SD = Standard deviation; * Statistically-significant at alpha = 0.05;
a. Adjusted changes, ratios, and *p*-values were adjusted for age, sex, race/ethnicity, education, number of sessions attended, and number of chronic conditions.

3.4.3. Effects of Baseline Characteristics on Medication Adherence

Baseline PHQ-8 score was significantly associated with changes in medication adherence from the baseline to the 6- and 12-month follow-up assessments ($F_{2, 739}$ = 3.83, *p*-value = 0.0222). Figure 4 shows change in medication adherence from baseline to the 6- and 12-month follow-up assessments by those with and without major depression at the baseline assessment. Both self-rated health and patient communication at baseline were not significantly associated with changes in medication adherence at the 6- and 12-month follow-up assessments (*p-value* > 0.05).

Figure 4. Changes in medication non-adherence from baseline to 6- and 12-month follow-up assessments among CDSMP participants with and without major depression at baseline (MMAS = Morisky Medication Adherence Scale)

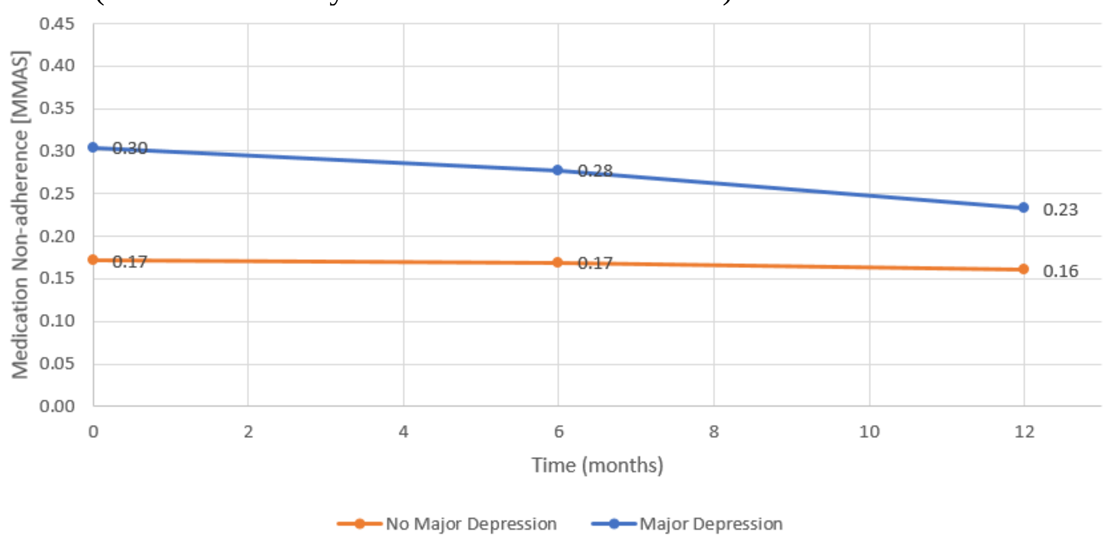


Table 6. Effects of the baseline-to-6-month changes in self-rated health, PHQ-8, or patient communication on the changes in medication adherence between 6- and 12-month follow-up assessments. [Regression coefficients for the interaction between time and the improvements after adjusting for the covariates (age, sex, race/ethnicity, education, number of attended sessions, and number of chronic conditions).]

Improvements during the first 6 months (the baseline to 6-month follow-up assessments)	**Overall (n=565)**			**Major Depression (n=101)**		
	MMAS-4	**Intentional Medication Non-adherence**	**Unintentional Medication Non-adherence**	**MMAS-4**	**Intentional Medication Non-adherence**	**Unintentional Medication Non-adherence**
Self-rated health	-0.0006	0.0191	0.0527	-0.0073	0.9591*	-0.1638
PHQ-8	0.0012	0.033	-0.0470	-0.0077	0.0870	-0.1704*
Patient communication	0.0059	0.1580	0.0584	0.0053	0.0697	0.0116

* Statistically-significant at alpha = 0.05; MMAS = Morisky Medication Adherence Scale

3.4.4. Effects of the First 6-month Changes on the Following 6-month Changes in Medication Adherence

Among the overall study population, the changes in self-rated health, communication with doctors, or PHQ-8 from baseline to 6-month follow-up assessment were not significantly associated with the changes in self-reported medication adherence from 6- to 12-month follow-up assessments) (p-value > 0.05) (Table 6). Among the study population with major depression at the baseline assessment, improvements in intentional medication non-adherence between the 6- to 12-month follow-up assessments was less for those who showed improvements in self-rated health (β = 0.9591, 95% CI = [0.0228, 1.8954], *p-value* = 0.0447) between the baseline and the 6-month follow-up assessment. Among the study population with major depression at the baseline assessment, the improvements in unintentional medication non-adherence during the final 6 months was greater for those who showed improvement in PHQ-8 (β = -0.1704, 95% CI = [-0.2792, -0.0616], *p-value* = 0.0021) during the first 6 months. All these regression results were adjusted for age, sex, race/ethnicity, education, number of attended sessions, and number of chronic conditions.

3.5. Discussion

In this study, the effects of CDSMP on medication adherence among the older participants was examined, and potential factors (e.g., baseline and first six-month changes in self-rated health, depression, and communication with doctors) that may contribute to the long-term changes in medication adherence among CDSMP participants was explored. Based on the extant literature, it was hypothesized that short-term improvements in self-rated health, depression, and communication with doctors would contribute to the long-term improvements in medication adherence. The changes from the baseline to the 6-month follow-up assessment were considered as the short-term changes, and the changes from the baseline to the 12-month follow-up assessment were considered as long-term changes.

Confirming the prior CDSMP evaluation papers [11, 12], this study showed that CDSMP had a statistically-significant long-term effect on medication adherence but not short-term effects. Compared to the previously published CDSMP national evaluation papers [11, 12], which included participants at ages 19 years and above, this study focused specifically on older adults population. This study reaffirms that the impacts of CDSMP observed in a general population holds true for this specific age group. A cognitive and behavioral intervention, such as CDSMP, may promote cognitive changes first, which then is followed by behavioral changes [33].

Furthermore, this study demonstrated that the program impacts primarily unintentional medication non-adherence rather than intentional medication non-adherence. Unlike intentional medication non-adherence, unintentional medication non-adherence is associated with lack of capacity or resources [34]. CDSMP educates its participants on skills and tools to handle stress, engage in healthy lifestyles, communicate with their family, friends, and physicians, and seek necessary resources. The acquirement of the skills and tools may be related to improvements in unintentional medication non-adherence, but not intentional medication non-adherence. Unintentional medication non-adherence is more prevalent in some health conditions, such as cardiovascular diseases [35], and the program may have particularly greater benefits among the population.

It was also observed in this study that the program effect on medication adherence among the participants with major depression at the baseline assessment would be significantly-greater than those without major depression at the baseline assessment. Depression is one of the most consistent determinants of medication non-adherence [13, 14]. Compared with the individuals without major depression, those with major depression are less likely to adhere to their medication at the baseline, hence more room for improvements. The finding implies that those with depressive symptoms can benefit more from CDSMP or similar programs with regard to adhering to their medication.

Among the participants with depressive symptoms, those who showed greater improvements in depression at the 6-month follow-up were more likely to show greater improvements in unintentional medication non-adherence from 6- to 12-month follow-up assessments. As discussed previously, the literature have consistently indicated the positive association between depression and medication non-adherence [13, 14]. Also, depression is associated with poorer cognition [15, 36]. Given this, it is not surprising to find the strong association between the improvement in depression and improvement in unintentional medication non-adherence. In addition, the longitudinal nature of the current study adds to the literature by introducing the 'time' component and enabling ordering of events. On the other hand, the improvements in intentional medication non-adherence during the final 6 months was less for the participants who showed improvement in self-rated health. Improved health can reduce perceived needs for the treatment, and thereby increasing the likelihood of intentional medication non-adherence [37, 38]. The perceived needs for the medication was higher among older adults who adherent to their medication treatments than those who reported intentional medication non-adherence [39].

There are some limitations to this study. First, the study relied on the self-reported data. The self-reported data cannot be verified and may be subject to various biases (e.g., social desirability bias). In addition, the MMAS-4 had a relatively low reliability for this population. However, self-reported data can also provide a rich insight about the context. For example, self-reported data on medication non-adherence could be classified into intentional versus unintentional medication non-adherence. Second, this study employed the secondary data analysis, and the study was limited by the availability of variables. The failure to include the important predictors in a regression analysis can lead to omitted variable bias and inaccurate statistical inferences. While the secondary data did not have all the key predictors of medication non-adherence (e.g., medication cost, patients' attitudes toward medication, characteristics of prescription, and characteristics of providers), the data had a good number of the known predictors (e.g., self-rated health, depression, and communication with doctors) for the initial exploration.

Despite the limitations, this study is one of the few studies that attempted to understand the underlying mechanism of the effect on medication adherence. Also, the secondary data was based on a pre-post longitudinal study design, hence allowed the examination of an over-time changes in the participants' medication adherence, as well as other influencing factors (e.g., self-rated health, depression, and communication with doctors).

3.6. Summary and Future Implication

The current study attempted to examine the long-term effects of CDSMP on medication adherence that has not been examined in detail previously. This study suggests that CDSMP improves overall medication adherence in a long-term, and primarily unintentional medication non-adherence. Unintentional medication non-adherence represents a primary form of medication non-adherence in older adults with one or more chronic conditions, and program such as CDSMP can be particularly more helpful among the population. This study also indicated that the long-term program impacts on medication non-adherence could be influenced through the short-term program impacts on other health and health-related indicators, such as self-rated health and depression. The limitations of the current study guides the future research, such that future research can be further enlightened by a more comprehensive examination that incorporates the key drivers of medication adherence.

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4. IMPACTS OF PATIENT'S ATTITUDES AND BELIEFS ON COST-RELATED MEDICATION NON-ADHERENCE AMONG OLDER ADULTS WITH CHRONIC DISEASES

4.1. Overview

Background: Cost-related medication non-adherence (CRN) can impact the management of chronic conditions prevalent in an aging population. Though patient attitudes have been identified as risk factors of CRN, limited data are available on interacting influences among poverty, patient attitudes, and CRN. The objective of this study was to examine the causal paths between poverty, patient attitudes, and CRN, based on the modified Proximal-Distal Continuum of Adherence Drivers Model.

Methods: The study included a nationally-representative sample of 4,818 individuals from the 2015 National Health Interview Survey data, 65-years or older, with the diagnosis of hypertension or diabetes and on prescription medication for at least one of these conditions. The structural equation modeling (SEM) was applied to the 2015 National Health Interview Survey data to examine whether perceived medication affordability, access to healthcare, and patient satisfaction influence the effects of poverty on CRN (skipped doses, took less doses, or delayed filling prescription to save money).

Results: The median age of the sample was 73-years, 55% were female, 92% were non-Hispanic, and 83% were White. Six percent of the participants reported CRN in the past 12-months. The model showed a good-to-fair fit, and all the paths were significant ($p<0.05$), except for age. The effects of poverty on CRN was mediated through the medication affordability, access to healthcare, and overall patient satisfaction.

Discussion: The study examined the direct and indirect effects of patients' attitudes, such as perceived medication affordability and patient satisfaction, on CRN and how patients' attitudes medicated the effects of poverty on CRN. We call for more senior-friendly public health interventions that can address these modifiable barriers in order to reduce CRN in older adults with chronic conditions.

4.2. Introduction

Medication non-adherence is a persistent public health issue that can influence management of chronic conditions, especially among older adults who are more likely to bear a greater disease burden than their younger counterparts. While there are many reasons for medication non-adherence, older adults may forgo medications due to cost-related concerns, such as prescription coverage and out-of-pocket costs [1-3]. This type of medication non-adherence is called cost-related medication non-adherence (CRN). CRN was observed in about ten to twenty percent of non-institutionalized older adults [4-6], and CRN was significantly more prevalent among older adults with multimorbidity (e.g., 43.1% among those with five or more chronic conditions versus 13.7% among those without any chronic conditions) [4], as well as those who fell in the "doughnut-hole" [2]. Ample evidence from the literature implies the adverse consequences of medication non-adherence, including poorer health, increased risk of mortality and greater healthcare costs [7-9].

Beyond the financial factors, past literature has also identified that CRN is associated with patients' characteristics (e.g., sociodemographic characteristics, health status, and attitudes) [10-12] and patients' relationship with their healthcare providers [13]. For example, Kurlander *et al.* [14] examined CRN among patients with diabetes on diabetic and pain medications. Kurlander *et al.* [14] showed that low-income status was associated with CRN for pain medications but not for diabetes medications. The same study also showed that depressive symptoms and negative treatment-related beliefs were associated with CRN for diabetes medication. These observations imply that CRN is likely to be influenced by both financial and non-financial determinants. The effects of financial determinants on CRN may be further augmented or diminished by non-financial factors, such as patients' attitudes and beliefs. In this study, it was hypothesized that perceived medication affordability, access to healthcare, and patients' satisfaction with healthcare services were drivers of CRN among older adults with chronic diseases.

Patient satisfaction is an attitude associated with evaluation of patient's experience with healthcare services [15, 16]. Mpinga and Chastonay [17] proposed that the major constructs of patient satisfaction include availability of services, accessibility of care (i.e., physical, economic, and information accessibility), participative healthcare, acceptability of cost (i.e., financial, physical, and cultural), and quality of care (e.g., competency and appropriate treatment and infrastructure). A comprehensive systematic review concluded that a positive association exists between patient satisfaction and medication adherence [18]. However, the review used a broad definition of patient satisfaction and did not examine how each of the constructs of patient satisfaction was related to medication adherence. Also, there is a lack of understanding of the association between patient satisfaction and medication adherence.

Medication affordability, a major construct of patient satisfaction [17], is a proximal driver of medication non-adherence under the Proximal-Distal Continuum of Adherence Drivers Model [19]. Based on a nationally-representative sample of adults with one or more chronic diseases, the odds of engaging in medication non-adherence among those with low medication affordability was almost four-times the odds of those with high medication affordability [19]. While medication affordability can be closely associated with diverse financial pressures (e.g., cost and resource availability), a study showed that medication affordability is not necessarily bound by the cost of prescription medication or financial resource availability [20].

Unlike medication affordability, relationship between medication adherence and physical access to healthcare has been under-studied. Based on the currently-available literature, physical access to care may have some, but relatively-weak effects on CRN. For example, previous studies showed conflicting findings about the relationship between the distance to a healthcare location (e.g., clinic or hospital) and medication adherence. A study did not find any statistically-significant relationship between treatment compliance and physical access to healthcare among pediatric kidney transplant population [21], but another study reported that the distance to clinic was a statistically-significant contributing factor to medication non-adherence in diabetic patients [22]. Long waiting time for meeting with healthcare providers was found to be associated with medication non-adherence among patients with hypertension and diabetes in South India [23]. The difference in the studies may be related to different characteristics of the study population and diverse aspects of physical access to healthcare.

In this study, the potential causal paths involving poverty, patient attitudes, and CRN were hypothesized based on the modified Proximal-Distal Continuum of Adherence Drivers Model [19]. The model hypothesized that overall patient satisfaction, perceived access to care, and perceived medication affordability will mediate the relationship between CRN and the distal driver (e.g., household poverty level and age), and mental health. Furthermore, the modified model also hypothesized that (1) low financial resources would adversely affect perceived medication affordability, access to care, and CRN; (2) improving perceived medication affordability or access to care would increase patient satisfaction; (3) poorer mental health would adversely affect perceived medication affordability and CRN; (4) older age would adversely influence medication affordability and access to healthcare; and (5) the strongest predictor of the CRN would be perceived medication affordability. Thus, the objectives of this study are to examine the effects of patient attitudes on CRN and to examine the mediating effects of patient attitudes on relationship between poverty and CRN.

4.3. Methods

4.3.1. Data Source

The data source for this research is the National Center for Health Statistics (NCHS)'s National Health Interview Survey (NHIS) was collected in 2015. The NHIS 2015 is a cross-sectional household interview survey that was designed to capture health and health-related information among the civilian noninstitutionalized population living in US at the time of assessment. The NHIS was collected via face-to-face interviews in a nationally-representative sample of households that had been sampled through a complex sampling design involving the use of an all-area sampling frame, state stratification, and differential sampling rates. The multistage sampling methods enabled the NCHS to be cost-efficient, yet still be able to select the representative sample of the target population. Furthermore, older black, Hispanic, and Asian adults (i.e., 65 years or older) had greater likelihood to be selected for the interview.

4.3.2. Study Participants

The target population of the NHIS 2015 was civilian noninstitutionalized populations living the US at the time of assessment, and the study participants were further narrowed down to those who self-reported: (1) being diagnosed with hypertension or diabetes; (2) having prescription medication for those conditions; and (3) being 65 years old or older at the time of the assessment. The survey participants were excluded from the study if the information about the sample adult was collected from a proxy. The study sample selection was performed based on the self-reported data.

4.3.3. Variables

CRN. Data were collected on three types of the CRN behaviors in the past twelve months: skipping medication doses to save money, taking less medicine to save money, or delaying filling a prescription to save money. Each of the three items was scored “yes” or “no.” A patients who reported an affirmative response to any of the three items was categorized as “having CRN”, and patients who did not report any affirmative response to all three items were categorized as “not having CRN.” Reliability of the measures was tested, and it was shown that high test-retest reliability (i.e.,$\kappa \geq 0.6$) [24]. These are also standard measures used in national surveys such as NHIS and Medicare Current Beneficiary Survey.

Medication unaffordability. Medication unaffordability was assessed using a single-item that asked: “during the past twelve months, was there any time when you needed (prescription medicines) but didn’t get it because you couldn’t afford it?” The item was scored “yes” or “no.”

Overall patient satisfaction. Patient satisfaction was assessed using a single-item that asked: “In general, how satisfied are you with the healthcare you received in the past twelve months?” The valid response ranged from “very satisfied” to “very dissatisfied,” with a higher score indicating greater satisfaction. Twenty-six (0.5%) of the study-eligible patients did not report on this variable because they did not receive any healthcare in the past twelve months.

Limited accessibility to care. Data were collected on the following five areas of accessibility to care in the past 12 months: (1) delayed getting care because of difficulty in getting through on the telephone; (2) delayed getting care because of difficulty in getting an appointment in a timely manner; (3) delayed getting care because of long wait times (at the healthcare setting); (4) delayed getting care because the (clinic/doctor's) office wasn't open when (the respondents) could get there; and (5) delayed getting care because of lack of access to transportation. Each item was scored "yes" or "no." A patient who reported "yes" to any of the five items was categorized as "experiencing poor accessibility to care," and a patient who reported "no" to all five items was categorized as "not experiencing poor accessibility to care". These are standard measures used in NHIS to examine accessibility to care since 1990s.

Financial resource. The ratio of family income to the poverty threshold was used to account for the total household size. The ratio of family income to the poverty threshold was categorized into four groups: less than 1.00, 1.00 – 1.99, 2.00-3.99, and 4.00 and over (based on 2014 poverty thresholds).

Mental health. The 2015 NHIS used the K6 screening scale for assessing the presence of serious mental illness (SMI). The K6 screening scale is composed of six 5-point Likert-items on how often respondents felt nervous, hopeless, restless or fidgety, depressed, needing effort on everything, and worthless in the past thirty days. For each item, the possible response ranged from "all of the time" (=1) to "none of the time" (=5), hence sum of the six K6 items could range from 6 to 30. Using the dichotomous scoring approach, as presented by Kessler *et al*. [25], the respondents with the sum of the K6 items being less than 19 were classified as “probably not having SMI” (=0), and the respondents with the sum of the K6 items being 19 or higher were classified as “probably having SMI” (=1). The Cronbach’s alpha for the scale was 0.84.

Demographic and sociodemographic information. The 2015 NHIS data included age, sex, race, ethnicity, education, and self-rated health. The age was categorized into “less than 75-years” or “75-years or older.” The dichotomization was guided by the data distribution, such that about half of the study sample was assigned in each category. Sex was classified as male versus female. Ethnicity was dichotomized as Hispanic versus non-Hispanic. Race was dichotomized as White versus non-White. Region was categorized into Northeast, Midwest, South, and West.

4.3.4. Analysis

Mean and standard deviation or frequency and percentage were used to describe characteristics of the study participants and examine missing data. Twenty-six percent (n=1,254) of the study-eligible patients had missing values on one or more of the variables included in the structural equation model (SEM). Overall, there were very few missing values (<5%) with most variables, but eighty-five percent (n=1,063) of these patients did not report all the income-related information to estimate the financial resources. Thereby, the final hypothesized model was also tested using multiple alternative measures of financial resources (e.g., ever concerned about having not enough food in the past twelve months) that had relatively lower missing rates. The result was not presented in this paper, but there was no meaningful difference between the analysis using the income variables and alternative variables.

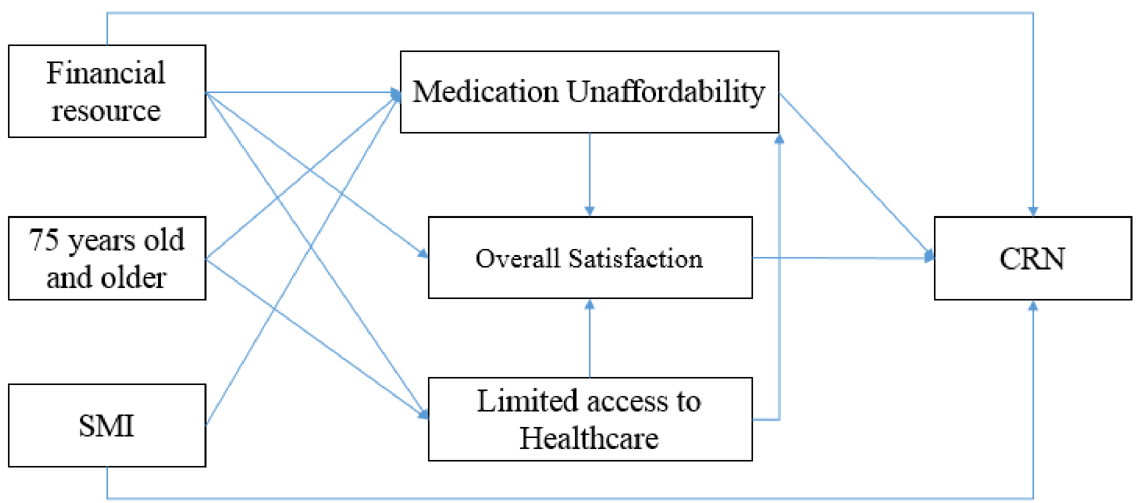
Using χ^2 test, being 75 and older, female, or non-White, living in Midwest, not having problem with access to healthcare, or having a SMI were positively associated with having one or more missing values on the SEM variables ($p<0.5$). Similarly, being 75 and older, female, or non-White, or living in Midwest were positively associated with missing data on poverty ($p<0.5$).

Structural equation modeling (SEM), after conducting the preliminary analyses, was used to test the hypothesized model. The conventional SEM steps were followed: model identification, parameter estimation, fit evaluation, and model re-identification. Robust maximum likelihood estimation method was used to account for non-normal, categorical endogenous variables. Chi-square test, confirmatory factor index (CFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR) were used for the fit evaluation. Non-significant Chi-square test, CFI above 0.95, RMSEA less than 0.05, and SRMR less than 0.05 were considered as an indication of a good-fit. RMSEA between 0.05 and 0.08 was considered as an indication of a fair-fit. Furthermore, modification indices were used to identify potential areas of the model that were poorly-fitting. The direct path between access to healthcare and CRN was dropped to obtain the better fit.

The final model for testing included a total of three exogenous variables (i.e., age, mental health, and poverty) and four endogenous variables (i.e., CRN, overall patient satisfaction, perceived access to care, and perceived medication affordability)

(Figure 5). The model was identified, because the model fulfilled the necessary condition for the model identification, *t-rule* (i.e., $t \leq (p)(p+1)/2$, where t = number of parameters to be estimated, and p=number of observed variables), and the recursive rules (i.e., no loops, no reciprocal causes among endogenous variables, and no correlated errors).

Figure 5. Hypothesized model depicting factors influencing cost-related medication non-adherence



SMI = Serious mental illness; CRN = Cost-related medication non-adherence

All statistical analyses in this study were performed with SAS 9.4. As instructed in the NHIS data guide, the subset analyses were performed using the complete data file to ensure correct estimation of variance and use of appropriate sampling weights.

4.3.5. Institutional Review Board

It has been confirmed from the Texas A&M University Institutional Review Board (IRB) that the study does not require any IRB approval for using a public use data set (https://vpr.tamu.edu/compliance/rcc/irb/irb-guidance/public-use-data-sets).

Table 7. Characteristics of the study participants (weighted by sampling weights).

Characteristics	**Weighted Median**
Age (years)	73
	Weighted %
Female	54.7
Non-Hispanic	91.7
Race	
White	83.0
Black/African American	11.1
Asian	4.0
Other races	0.6
Multiple races	1.3
Married or living with a partner	55.9
Region	
Northeast	18.9
Midwest	23.0
South	39.5
West	18.6
Having diagnosed with hypertension only	38.1
Having diagnosed with diabetes only	5.0
Having diagnosed with both hypertension and diabetes	26.7
Cost-related medication non-adherence (CRN)	6.0

4.4. Results

4.4.1. Study Participants

The final study sample included 4,818 older adults with hypertension or diabetes. Six percent of the study sample reported CRN in the past twelve months. The median age of the study sample was 73-years old, and the majority were female (54.7%), non-

Hispanic (91.7%), and White (83.0%) (Table 7). Forty-two percent of the sample were married or lived with a partner at the time of assessment.

4.4.2. Model Fit

The tested model had a good-to-fair fit based on the three fit indices: CFI (0.9709), RMSEA (0.0588), and SRMR (0.0259). The Chi-square test was statistically-significant (Chi-square = 66.6741, df = 5, $p < 0.0001$), which indicates a poor-fit. However, Chi-square test of fit can be sensitive to trivial deviations from the perfect-fit with a sufficiently-large sample size. Despite the adequate fit of the model, CRN remained largely unexplained with about 34.3% of the explained variance.

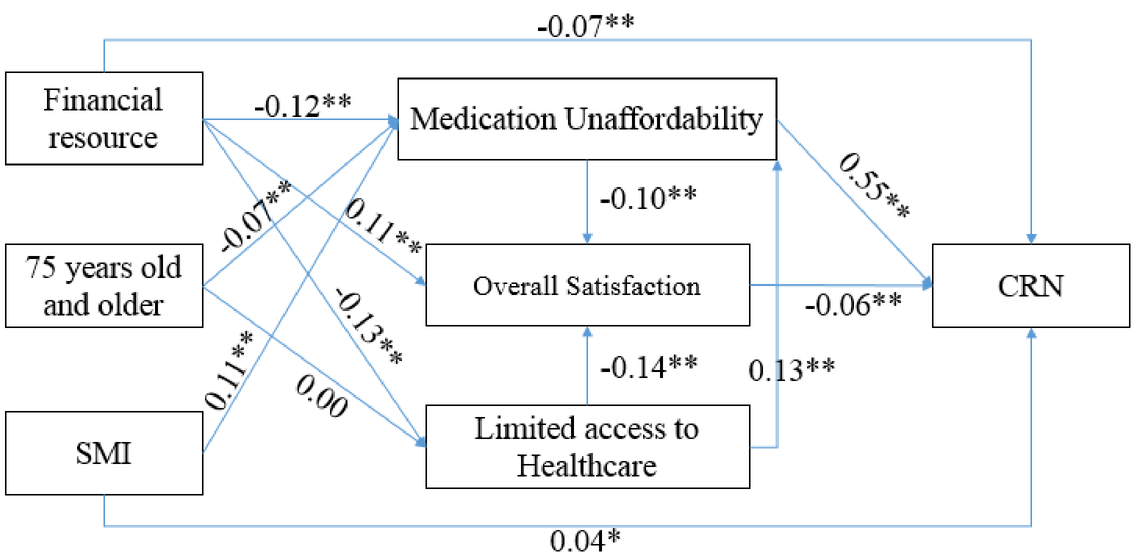
4.4.3. Path Coefficients

Table 8 and Figure 6 present the standardized path coefficients of the tested model. Greater likelihood of CRN was associated with poorer perceived-medication affordability (β = 0.55), lower patient satisfaction (β = -0.06), less financial resources (β = -0.0720), and presence of SMI (β = 0.0442). Poor perceived medication affordability was associated with perceiving difficulty in access to care (β = 0.1259), lower ratio of family income-to-poverty threshold (β = -0.1209), presence of SMI (β =0.1051), and younger age (β = -0.0683). Lower patient satisfaction was associated with poorer perceived medication affordability (β = -0.0988), poorer perceived access to care (β = -0.1423), and less financial resources (β =0.1090). Poorer perceived access to care was associated with less financial resources (β = -0.1250). Effects of age on perceived access to care was not statistically-significant (p = 0.8390).

Table 8. Standardized path coefficients

Paths	Standardized β	Standard error	*p*-value
Medication unaffordability → CRN	0.5500	0.0118	<.0001
Overall satisfaction → CRN	-0.0633	0.0138	<.0001
Financial resource → CRN	-0.0720	0.0139	<.0001
SMI → CRN	0.0442	0.0138	0.0013
Limited access to care → Medication unaffordability	0.1259	0.0163	<.0001
Financial resource → Medication unaffordability	-0.1209	0.0166	<.0001
SMI → Medication unaffordability	0.1051	0.0164	<.0001
Age (Being 75 years or older) → Medication unaffordability	-0.0683	0.0164	<.0001
Medication unaffordability → Overall satisfaction	-0.0988	0.0165	<.0001
Limited access to care → Overall satisfaction	-0.1423	0.0164	<.0001
Financial resource → Overall satisfaction	0.1090	0.0165	<.0001
Financial resource → Limited access to care	-0.1250	0.0166	<.0001
Age → Limited access to care	0.0034	0.0167	0.8390

Figure 6. Path diagram of the final structural equation modeling



* $p < 0.05$

** $p < 0.0001$

NS $p \geq 0.05$

SMI = Serious mental illness; CRN = Cost-related medication non-adherence

Table 9. Standardized total, direct, and indirect effects

Predictor	Through	Causal effect		
		Total	Direct	Indirect
Medication unaffordability	-		0.5500	-
	Overall satisfaction		-	0.0062
	Total	0.5562	0.5500	0.0062
Financial resource	-		-0.0720	-
	Medication unaffordability		-	-0.0665
	Overall satisfaction		-	-0.0069
	Medication unaffordability → Overall Satisfaction		-	-0.0008
	Limited access to healthcare → Medication unaffordability		-	-0.0087
	Limited access to healthcare → Medication unaffordability → Overall satisfaction		-	-0.0001
	Limited access to healthcare → Overall satisfaction		-	-0.0011
	Total	-0.1561	-0.0720	-0.0841
Having serious mental illness (SMI)	-		0.0442	-
	Medication unaffordability		-	0.0578
	Medication unaffordability → Overall satisfaction		-	0.0007
	Total	0.1027	0.0442	0.0585
Limited access to healthcare	Overall satisfaction		-	0.0090
	Medication unaffordability		-	0.0693
	Medication unaffordability → Overall satisfaction		-	0.0008
	Total	0.0791	-	0.0791
Overall satisfaction	-		-0.0633	-
	Total	-0.0633	-0.0633	-
Age (75 years or older)	Medication unaffordability		-	-0.0376
	Medication unaffordability → Overall Satisfaction		-	-0.0004
	Total	-0.0380	-	-0.0380

4.4.4. Total, Direct, and Indirect Effects

Table 9 presents the total, direct, and indirect effects of the model. Medication unaffordability had the strongest total effects on CRN, followed by financial resources, presence of SMI, limited access to healthcare, and overall satisfaction. Age had the least total effects on CRN. Approximately half of the effects of financial resources on CRN were mediated through medication unaffordability, limited access to healthcare, and overall satisfaction (direct effects = -0.0720; indirect effects = -0.0841).

4.5. Discussion

In this study, the causal paths between financial resources, patient's attitudes, and CRN were explored based on the extended Proximal-Distal Continuum of Adherence Drivers Model. As hypothesized under the conceptual framework, perceived affordability was the strongest predictor of CRN, and this finding is consistent with the prior research [19]. From a national sample of adults with one or more chronic conditions, McHorney and Spain [26] found that medication affordability is the most common reason for medication non-adherence (about 50%). In agreement with the current study finding, McHorney *et al.* [19] found that the odds of engaging in medication non-adherence among those with the least perceived affordability was significantly-greater than the odds among those with the highest perceived affordability. The difference between their study and the current study is that their study looked at overall medication non-adherence among the general population, while the current study focused only on cost-related medication non-adherence among older adults. The current study reaffirms the previous finding and strengthens the evidence.

The current study demonstrated that the effects of poverty on CRN were mediated through patient's attitudes, such as perceived medication affordability, perceived access to care, and patient satisfaction. Extant studies suggest that the relationship between financial pressure and medication non-adherence is complex, and financial pressure cannot solely explain the behavior. For example, in the Piette's study [20], there was a substantial variation in CRN for preventive versus symptom-relief medication types among middle-aged and older adults with chronic diseases. Piette *et al.* [20] found that patients were significantly more likely to report CRN on symptom-relief medication than on preventive medications. Such an observation is potentially attributed to the differences in patients' attitudes towards different medication types.

In a separate study, Piette *et al.* [27] showed that CRN was observed in both low- and high-income populations, and that having low perceived need for medication and perceived medication concerns (e.g., side effects) were positively associated with CRN in both low- and high-income populations. In their study, Piette *et al.* [27] examined not only the effects of patients' attitudes, but also the effects of depression. Similar to our study, they found the significant association between depression and CRN. The difference between their and our study is that while their study focused on independent effects of patients' attitudes and depression on CRN by the degree of financial pressure, the current study focused on the causal paths that link these multiple factors together.

In this study, satisfaction with overall healthcare services was adversely associated with CRN. This is consistent with the previous findings. Oetzel *et al.* [28] indicated a weak, positive correlation between patient satisfaction and medication adherence among patients with HIV/AIDS ($r = 0178$, $p < 0.05$). However, their studies did not examine the independent effects of patient satisfaction on medication non-adherence, and the study population was different from the current study. In the current study, access to healthcare (non-financial) had weak indirect effects on CRN via medication affordability and patient satisfaction but did not have any direct effects on CRN. This potentially explains the conflicting findings in the literature about the relationship between access to healthcare (non-financial) and CRN.

As hypothesized under the Proximal-Distal Continuum of Adherence Drivers Model, age had a relatively weaker effect on CRN compared to other variables examined in the model. The observation is not surprising considering that the past literature has shown conflicting findings about the relationship between age and medication non-adherence. For example, two studies about medication adherence to adjuvant hormonal therapy in breast cancer patients showed conflicting findings about age: one study indicated older age (i.e., > 70 years old) as a potential barrier to medication adherence [29]; but another study indicated younger age (i.e., < 70 years old) as a potential barrier to medication adherence [30]. A systematic review indicated that extremes of age (i.e., younger than 45-50 years old or older than 65-75 years old) was largely and negatively associated with medication adherence [31]. However, the findings of the review focused specifically on female breast cancer survivors who were on adjuvant hormonal therapy, hence their findings may not be generalizable to a different population.

This study has some limitations. First, the cross-sectional nature of the data limits examination of the hypothesized causality, and the SEM approach permeates testing of the causality that was hypothesized based on the past literature. Second, the study relied on the self-reported data, and, hence, the reported information cannot be verified. However, self-reported data on medication non-adherence can be rich with contextual information and enable researchers to identify types of medication non-adherence (e.g., intentional versus unintentional and cost-related versus not cost-related). Third, this survey had only a single item on satisfaction with healthcare, and the variable response was highly skewed. While the patient satisfaction measure was complemented by using separate measures of perceived access to care, the study still lacks the data on other dimensions of patient satisfaction. Fourth, the tested model did not include some potentially-important drivers, such as perceived need and concerns for medication. The model explained only about one-third of the variance of CRN, and inclusion of other important determinants may further improve the model's explanatory power. Lastly, the listwise deletion approach was used for handling the missing data, and more than 25% of the cases were omitted under this approach. Those who did not report any problems with access to healthcare services were more likely to be omitted from the analysis, and, therefore, the likelihood of having access to healthcare services would have been biased downward under the approach. Also, using the listwise deletion approach tends to result in larger standard errors and wider confidence intervals due to lower power. To overcome this limitation, the structural equation model was performed with alternative financial resource-related variables (e.g., concerned about running out of food) that had low missing rate, and there was no meaningful change to the results (i.e., no changes in statistical significance and minimal changes in regression coefficients).

Despite these limitations, this study has some strengths. First, this is one of the few studies that attempted to explore the causal paths between financial resource and CRN and to understand the potential effects of patient attitudes on the relationship. Second, this study used a nationally-representative dataset.

4.6. Summary and Future Implication

The current study attempted to provide an explanation for the relationship between financial pressure, patients' attitudes (e.g., perceived medication affordability, access to care, and patient satisfaction), and CRN that have not been examined previously. The study findings suggest that perceived medication affordability is the key driver of CRN, and effects of poverty on CRN is mediated through patients' perceived medication affordability, perceived access to care, and satisfaction with healthcare. While multiple possible pharmaceutical policy reforms (e.g., government's active involvement in determining prescription-drug price) should be discussed for addressing the financial-related factors that drive medication non-adherence [32], there are many uncertainties at this stage of health policy turmoil. Meanwhile, this study finding implies that CRN in older adults can not only be reduced by reducing their financial pressure but also by modifying their attitudes. In addition to the need for senior-friendly public health interventions that address these modifiable barriers in older adults with chronic conditions, the study limitations also suggest future studies that can test more comprehensive models. More comprehensive models should include not only the patient-related factors but also provider-, prescription-, and system-related factors.

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5. SUMMARY AND CONCLUSIONS

Use of pharmacotherapy or medication treatment has become more prevalent in the US over the past decades. Poor medication adherence is a persistent public health challenge associated with treatment ineffectiveness and adverse health outcomes, increased healthcare costs, and even death. This dissertation was proposed and completed under the hypothesis that medication non-adherence is influenced by multiple modifiable factors and can be improved.

The interaction between patients and their healthcare providers is one of the most important social activities that can influence the patients' chronic disease self-management behavior, including medication adherence. However, the patient-provider interaction can be described in many ways, such as affective or instrumental interaction. Understanding how different aspects of a patient-provider interaction are related to medication adherence will enable the formulation of effective medical interaction strategies for reducing medication non-adherence. Hence, the first study of this dissertation was a systematic literature review aimed at summarizing the prevalence of medication non-adherence among community-dwelling older adults, as well as providing an overview of the association between the different aspects of patient-provider relationship and medication adherence among community-dwelling older adults. Through the comprehensive literature search, ten articles with a total sample size of 25,010 patients were included in this systematic literature review. The reported medication non-adherence rate ranged from 14% to 52%, with the mean medication non-adherence rate of 33%. This is similar to the previously-reported medication non-adherence rates in other reviews. The reported medication non-adherence rate was higher in the non-US countries (45%) than in US (33%). Most of the studies focused on the instrumental interaction type, such as information exchange. While information exchange was positively associated with the patients' medication adherence, discussion about barriers or making adherence easier was negatively associated with patients' medication adherence. It would be important to understand the context and dynamic nature of the medical interaction beyond the snapshot to properly interpret the observed relationship. There is a need for studies that utilize longitudinal research design or complex dynamic systems science perspective. Furthermore, the evidence was weak and suggests opportunities for more vigorous researches. For example, using multiple standardized medication adherence measurements of medication adherence can produce stronger evidence that can be summarized and compared.

The second study of this dissertation aimed at exploring and evaluating the long-term effects of an evidence-based cognitive and behavioral intervention on medication adherence among older adults. Given that prior research indicated that complex interventions with multiple components had a greater likelihood of success in improving medication adherence, we chose the Chronic Disease Self-Management Program (CDSMP) for the study. Not only has CDSMP been widely disseminated and implemented in multiple community settings, it has also been shown to be successful in improving medication adherence among its participants in long-term. This second study went beyond prior investigation of the long-term effects of CDSMP on medication adherence among the older participants to examine the potential effects of other determinants of medication adherence, such as self-rated health, depression, and communication with doctors, on the program impacts. It was hypothesized that the short-term effects of CDSMP on self-rated health, depression, and communication with doctors could influence medication adherence in long-term.

Using the national CDSMP evaluation data, this second study showed that CDSMP had a statistically-significant long-term effect on medication adherence among the older participants but not short-term effects, confirming the prior findings. There are three key observations from this study to be highlighted. First, this study showed that the improvements in medication adherence were largely contributed by the improvements in unintentional medication non-adherence, rather than intentional medication non-adherence. This implies the importance of understanding the differences between intentional and unintentional medication non-adherence and the needs for different approaches to address the different types of medication non-adherence. Second, the older participants who had depressive symptoms at the baseline showed the greater improvements in medication adherence than those without depressive symptoms at the baseline. Along with the first key observation, this finding has important implications for the program recruitment, as well as for future research. Interventions, such as CDSMP, can be more beneficial to a population with a greater likelihood of unintentional medication non-adherence or a population with depressive symptoms. Third, the hypothesis that the short-term effects of CDSMP on self-rated health, depression, and communication with doctors could influence medication adherence in long-term was partially supported. The changes in self-rated health and depression during the first six months from the baseline assessment moderated the changes in medication adherence during the last six months from the six-month follow-up assessment. Improving depression during the first six months was associated with a greater improvement in unintentional medication non-adherence during the last six months. On the other hand, improving self-rated health during the first six months was associated with a greater engagement in intentional medication non-adherence during the last six months. Understanding for the underlying mechanism of the program impacts on medication adherence will enable better targeting, as well as supplementing the program for better outcomes. For example, highlighting the importance of medication adherence regardless of improved health status may prevent the older participants from engaging in intentional medication non-adherence after their health improved. Furthermore, this finding, again, highlights the potential need for different approaches to address intentional and unintentional medication non-adherence.

The third study of this dissertation focused on cost-related medication non-adherence (CRN). While financial factors are thought to be the main drivers of CRN, CRN is also influenced by the patient's characteristics, such as sociodemographic characteristics and attitudes, and the patient's health condition. In this study, the potential causal paths involving poverty, patient attitudes, and CRN were hypothesized based on the modified Proximal-Distal Continuum of Adherence Drivers Model, and tested using the structural equation model using the 2015 National Health Interview

Survey. The final model had a good-to-fair fit. Poorer perceived-medication affordability, lower patient satisfaction, less financial resources, and the presence of serious mental illness predicted a greater likelihood of CRN. Medication affordability was the strongest predictor of CRN, followed by financial resources, the presence of serious mental illness, access to healthcare, and patient satisfaction. Furthermore, about half of the effects of financial resources on CRN was mediated through patients' attitudes. This study can inform future interventions for improving CRN by the application of behavioral strategies to modify older adults' perceptions and attitudes. Future research can also be deigned to overcome some of the current study's limitation (e.g., inclusion of other proximal factors that are known to be strongly associated with CRN).

In summary, this dissertation reaffirmed that changes in medication adherence is associated with multiple factors that may also be associated with one another. What this also suggests is the need for future studies that can examine the complex nature of this mechanism that is likely to be beyond a linear relationship between just one factor and medication adherence. Understanding and acting upon this complexity can contribute to intervention implementation and dissemination.

APPENDIX A

SUMMARY OF THE TEN STUDIES INCLUDED IN SECTION 2

(SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS)

Table A1. Summary of the studies included in the current systematic literature review

Studies	**Medication adherence measurements**	**Patient-provider relationship (PPR) measurements**	**Control variables**	**Prevalence of medication adherence**	**Estimated association between medication adherence and measurements**
(Study reference, country, total sample size (n), chronic diseases, types of provider)	*(Data collection method (reported by whom); definition of measures; measure range (interpretation of the measure))*	*(Data collection method (reported by whom); definition of measure; measure range (interpretation of the measure))*			*(Performed analyses, reported metrics, reported metric values, direction of effect)*
Heisler *et al*, 2007 - US - n = 1558 - Diabetes - Physicians	-Self-reported (patients); -Difficulty in following diabetes medication as prescribed in the past 6 months; -ranged from 0-100 (higher = better)	- Self-reported (patients); - Provider's information provision from the ABIM and patient's involvement in decision-making from the PACIC scale - Each measure ranged from 0-100 (higher = better)	Age, sex, ethnicity, education, income, medical regimen, diabetes comorbidity, diabetes duration, and duration of PPR.	Not reported	- Multivariate linear regression - Standardized regression coefficients ($\beta_{standardized}$) - $\beta_{standardized}$ = 0.13* (Positive; medication adherence and provider's information provision) - $\beta_{standardized}$ = 0.03 (No difference; medication adherence and

Table A1. (Continued)

Studies	Medication adherence measurements	Patient-provider relationship (PPR) measurements	Control variables	Prevalence of medication adherence	Estimated association between medication adherence and measurements
					patient's involvement in decision-making)
Kressin *et al*., 2007 - US - n = 793 - BP (blood pressure) - Doctors	- Self-reported (patients); - Forgetting to take medication, not taking medications on purpose, taking less medications because of perceptions that one needed less, and having difficulties taking medication as prescribed - Binary (Non-adherent (=0) if reported any problem to at least 1 of the medication adherence items)	- Self-reported (patients); - Having patient-doctor discussion about making it easier to take your BP meds - Binary (1 = Yes)	Race, self-efficacy in taking BP as prescribed, told to split any BP pills by providers, perceived BP status, and site of care	77%	- Multivariate logistic regression - Odd ratio (OR) - OR = 0.56* (Negative)
Wilson *et al*., 2007 - US - n = 17569 - Did not focus on a specific health condition - Physicians	- Self-reported (patients); - CRN, non-adherence because of medication experiences (e.g., side effects), non-adherence because of self-assessed need for medication in the past 12 months	- Self-reported (patients); - Any patient-physician dialogue in the past 12 months about medication costs and changing a medicine because of patients' medication experience	None	60%	- Performed analysis was unclear - Proportions (e.g., among those who had patient-physician dialogue about changing prescription due to patients' medication experience (40%), 52% reported the

Table A1. (Continued)

Studies	Medication adherence measurements	Patient-provider relationship (PPR) measurements	Control variables	Prevalence of medication adherence	Estimated association between medication adherence and measurements
	- Binary (Non-adherent if reported any problem to at least 1 of the medication adherence items)	- Each measure was binary (1=Yes)			medication non-adherent.) - Negative[a]* (for both types of patient-physician dialogues)
Donohue *et al*., 2009 - US - n = 1001 - Did not focus on a specific health condition - Doctors	- Self-reported (patients); - CRN in the past 12 months - Binary (CRN (=1) if reported any CRN problem)	- Self-reported (patients); - Trust doctor to provide price-related information - Dichotomized (1 = trust)	Age, sex, race/ethnicity, education, marital status, income, number of drugs, drug spending, and drug insurance coverage	- Not reported	- Multivariate logistic regression - OR - OR = 0.71 (No difference; among those who reported not having a problem with drug costs) - OR = 0.77 (No difference; among those who reported having a problem with drug costs)
Turner *et al*., 2009 - US - n = 202 - BP - Doctors or nurses	- Self-reported (patients); - Last time missing any BP medication - Dichotomized (Non-adherent if missed any dose within the past 3 months)	- Self-reported (patients); - Patient's perception of how often his/her doctor/nurse listened careful to the patient - Dichotomized (1 = Yes)	age, race/ethnicity, number of bp meds, general health, mood disorder, check bp at home, not aware of medicare part d, had to go without usual bp med because not covered, running out of pills sometimes, trouble following doc's advice about taking meds, feel	78%	- Multivariate logistic regression - OR = 1.04 (No difference)

Table A1. (Continued)

Studies	Medication adherence measurements	Patient-provider relationship (PPR) measurements	Control variables	Prevalence of medication adherence	Estimated association between medication adherence and measurements
			unimportant to fill prescription quickly, important to talk about bp with doc/nurse, bp knowledge		
Luz *et al*., 2011 - Brazil - n = 1017 - Did not focus on a specific health condition - Physicians	- Self-reported (patients); - CRN in the past 30 days - Binary (CRN (=1) if reported any CRN problem)	- Self-reported (patients); - Frequency of patient-physician dialogue about health/treatment - Dichotomized (1 = rarely/never having patient-physician dialogue about health/treatment)	None	Not Reported	- Pearson's chi-square test - Prevalence ratio (PR) - PR = 2.72 (No difference)
Guz *et al*., 2013 - Philippine - n = 325 - Did not focus on a specific health condition - Doctors	- Self-reported (patients); - Morisky Mdication Adherence Scale (MMAS-8) - Trichotomized into high, medium, and low adherence	- Self-reported (patients); - Patients' trust in their physicians - Binary (1 = Trust)	(Not control variables, but other predicting variables in the SEM: patients' consultation satisfaction, depression, memory load, number of medical conditions, external memory strategy, event-based memory task)	59%[b]	- Structural equation modelling - Regression coefficients[c] (β) = 1.168* (Positive)
Halt *et al*., 2013 - US - n = 2194 - BP	- Self-reported (patients); - MMAS-8	- Self-reported (patients);	Age, race, marital status, education, comorbidity, reduced BP medications	86%	-Multivariate logistic regression

Table A1. (Continued)

Studies	Medication adherence measurements	Patient-provider relationship (PPR) measurements	Control variables	Prevalence of medication adherence	Estimated association between medication adherence and measurements
- Did not focus on a specific provider type	- Dichotomized (1 = Non-adherent)	- Patients' satisfaction with communication with providers - Binary (1 = Not satisfied)	because of cost, lifestyle modifications, depression, sexual functioning, BMI		- OR = 1.16 (No difference; among men) - OR = 1.75 (Positive; among women)
Jin *et al*., 2016 - Republic of Korea - n = 160 - Did not focus on a specific health condition - Pharmacists	- Self-reported (patients); - Adherence to Refills and Medication Scale (ARMS) - Ranged 12-48 (lower = better adherence) (Non-adherent if the score is 20 or higher)	- Self-reported (patients); - Patient-pharmacist relationship and communication (dissatisfaction/ neutral/ satisfaction) - Pharmacists' explanations of medication (none/ a little/ none)	age, education level, health-related problems, health literacy, frequency of doses, satisfaction with pharmacist's counseling, and (patient-pharmacist relationship and communication or explanation of medication)	48%	- Multivariate linear regression - Unstandardized regression coefficients ($\beta_{unstandardized}$) - $\beta_{unstandardized}$ = 0.022 (No difference; patient-pharmacist relationship and communication) - $\beta_{unstandardized}$ = -2.945 (Positive; explanation of medication)
Lee *et al*., 2017 - US - n = 191 - BP - Physicians	- Self-reported (patients); - MMAS-8 - Ranges from 0-8 (higher = better adherence)	- Self-reported (patients); - Quality of information exchanged from PCAS - ranges from 25-100 (higher = better informative communication)	Age, sex, education, race, income, live alone marital status, comorbidity class	Not reported	- Multivariate linear regression - $\beta_{standardized}$ = 0.25* (Positive)