ASSESSING SUSTAINED AND DIFFERENTIAL IMPACTS OF NORTH CAROLINA'S
MEDICAID "LOCK-IN" PROGRAM

Rebecca Boyd Naumann

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2017

Approved by:

Stephen Marshall

Nisha Gottfredson

Jennifer Lund

Christopher Ringwalt

Asheley Skinner

ABSTRACT

Rebecca Boyd Naumann: Assessing Sustained and Differential Impacts of North Carolina's
Medicaid "Lock-In" Program
(Under the direction of Stephen Marshall)

Between 2000 and 2015, half a million people died from a drug overdose in the U.S., and most of these deaths involved an opioid. Medicaid beneficiaries are a particularly high-risk population. One strategy that nearly all states use to address potential misuse of prescription opioids, and other controlled substances (CS), are Medicaid "lock-in" programs (MLIPs). MLIPs identify beneficiaries demonstrating potential overutilization of CS and control their access. In North Carolina (NC), beneficiaries enrolled in the MLIP are required to use a single prescriber and pharmacy to obtain specific CS for a 12-month period. There has been little research examining the impact of MLIPs.

In this dissertation, we 1) examined the sustained impact of the NC MLIP on dispensed CS and dosages of opioids dispensed (in terms of morphine milligram equivalents (MMEs)) and 2) examined whether trajectories of MMEs differed across time prior to, during, and following release from the MLIP for different strata of the population. Data included NC Medicaid claims linked to records from NC's Prescription Drug Monitoring Program from October 2009 through June 2013.

We found that compared to a period of stable CS dispensing prior to MLIP enrollment, the MLIP reduced the average numbers of CS dispensed both during lock-in and following

release. However, the program was also associated with increased acquisition of dispensed CS using non-Medicaid payment (e.g., out-of-pocket) both during lock-in and following release. Moreover, beneficiaries acquired greater MMEs of dispensed opioids from both Medicaid and non-Medicaid payment sources during lock-in and following release.

Considerable heterogeneity existed in trajectories of MMEs of dispensed opioids across time prior to, during, and following release from the MLIP. Five trajectory patterns appeared to sufficiently describe this underlying heterogeneity. All patterns demonstrated a spike in MMEs in the six months prior to lock-in, constituting a trigger for MLIP enrollment; however, patterns were dissimilar in overall starting values and slopes. While the trajectories indicated that the MLIP may have had little influence on MME patterns across time, strong associations between trajectory patterns and beneficiary characteristics were evident. Findings from this dissertation thus provide a foundation for informing future MLIP improvements.

To my husband, Tom, for his unwavering support, endless optimism, and fantastic sense of humor. I could not have done this without you.

"In life it's not where you go, it's who you travel with."- Charles Schultz

ACKNOWLEDGEMENTS

This dissertation would not have been possible without the support of several individuals. Thank you to my advisor throughout these last four years, Steve Marshall, for your mentorship, support, and encouragement. I am so grateful for the energy and time you spent creating opportunities for me to grow as a scientist. I owe a huge thank you to my other dissertation committee members—Nisha Gottfredson, Jenny Lund, Chris Ringwalt, and Asheley Skinner. Your wisdom, guidance, and reassurance helped shape not only the work on this dissertation but also me as researcher. Thank you to Krista Kness, at the NC Division of Medical Assistance, and Drew Roberts for their willingness to answer my many questions about the Medicaid "lock-in" program and NC Medicaid claims data.

There are several other people who helped create an encouraging, supportive, and fun environment throughout my time as a UNC PhD student. A big thank you to my colleagues at the UNC Injury Prevention Research Center—especially Meghan Shanahan, Maryalice Nocera, Tonya Watkins, and Paula Gildner—for their humor and continuous support. To current and previous injury epidemiology PhD students—Karen Roos, Jared Parrish, Apostolos Alexandridis, Katie Harmon, Jenny Jones, Rebecca Yau, Mackenzie Herzog, and Katie Wolff— thank you for helping to create such a welcoming and encouraging graduate school environment. I especially need to thank Anna Austin for the countless hours spent discussing latent class methods, as well as other research methods, throughout this dissertation process. Finally, a big

thank you to my friends in the PhD epidemiology program. I couldn't have asked for a better cohort to learn from and with.

Lastly and most importantly, I would not have reached this point without my family. To my parents, thank you for your countless sacrifices, unconditional love, patience, and encouragement. To my brother and sister, thank you for providing a regular source of inspiration for what it means to work hard and follow your dreams. And to my husband and two sons, for making me laugh every day and remember the bigger picture.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AHRQ   Agency for Healthcare Research and Quality

AIC   Akaike's Information Criterion

BCN   Blue Care Network

BIC   Bayesian Information Criterion

CCS   Clinical Classification Software

CCW   Chronic Conditions Data Warehouse

CD   Count Difference

CDC   Centers for Disease Control and Prevention

CMS   Centers for Medicare and Medicaid Services

CPT   Current Procedural Terminology

CS   Controlled Substances

CSRS   Controlled Substances Reporting System

DHHS   Department of Health and Human Services

DMA   Division of Medical Assistance

DPH   Division of Public Health

DRIVE   Data Retrieval Information and Validation Engine

ED   Emergency Department

GEE   Generalized Estimating Equations

ICD-9-CM   International Classification of Diseases, Ninth Revision, Clinical Modification

LCGA   Latent Class Growth Analysis

LIP   "Lock-in" Program

LRT	Likelihood Ratio Test
MAT	Medication-assisted Treatment
MCO	Managed Care Organization
MD	Mean Difference
MLIP	Medicaid "Lock-In" Program
MME	Morphine Milligram Equivalents
MMIS	Medicaid Management Information System
NC	North Carolina
NDC	National Drug Code
NY	New York
PDMP	Prescription Drug Monitoring Program
REMS	Risk Evaluation and Mitigation Strategy
ssBIC	sample-size adjusted Bayesian Information Criterion
UNC	University of North Carolina

CHAPTER 1 – INTRODUCTION

Prescription drug overdoses have become a public health epidemic with enormous health, social, and economic impacts. Prescription drug overdose deaths have rapidly escalated over the past several years (Figure 1.1).[1] Between 2000 and 2015, the annual U.S. prescription drug overdose death rate tripled from 2.8 to 9.2 deaths per 100,000 population. Of the 29,728 lives lost to prescription drug overdoses in 2015, three out of four (76%) deaths involved an opioid analgesic (i.e., painkiller) and nearly one-third involved a benzodiazepine, a prescription drug often used in the treatment of anxiety.[1] (Note: some overdoses involve more than one type of drug).

Figure 1.1 Age-adjusted prescription drug overdose death rates per 100,000 population per year, United States, 2000-2015
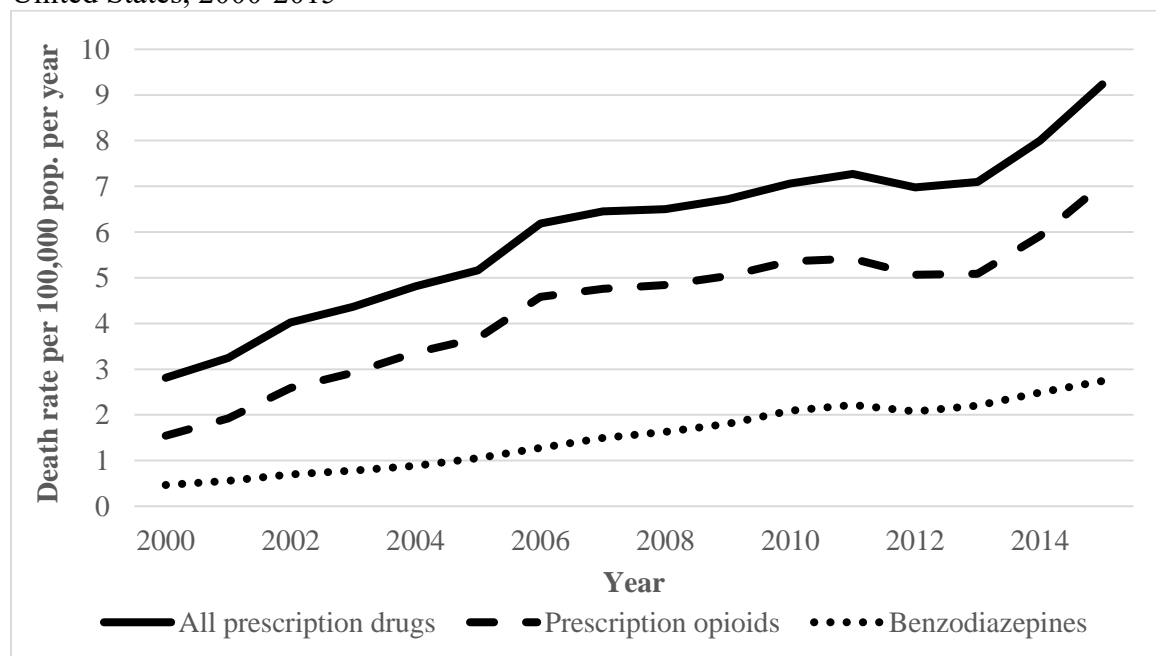
While prescription drugs, including opioids and benzodiazepines, play a legitimate and important role in pain management, particularly for palliative care, endemic misuse and abuse of these drugs has become a major public health problem, and arguably the defining public health crisis of the early 21st century. In 2011, approximately 1.4 million emergency department (ED) visits in the U.S. were related to the nonmedical use of prescriptions,[2] and in the year 2013 alone, prescription opioid overdose, abuse, and dependence cost the U.S. more than $78 billion in terms of health care costs, productivity losses, and criminal justice fees.[3]

The drug overdose epidemic in North Carolina (NC) has followed national trends, with NC also experiencing a substantial increase in fatal overdoses over the last several years (Figure 1.2).[4]

Figure 1.2 Drug overdose death rates per 100,000 population per year, North Carolina, 2000-2015
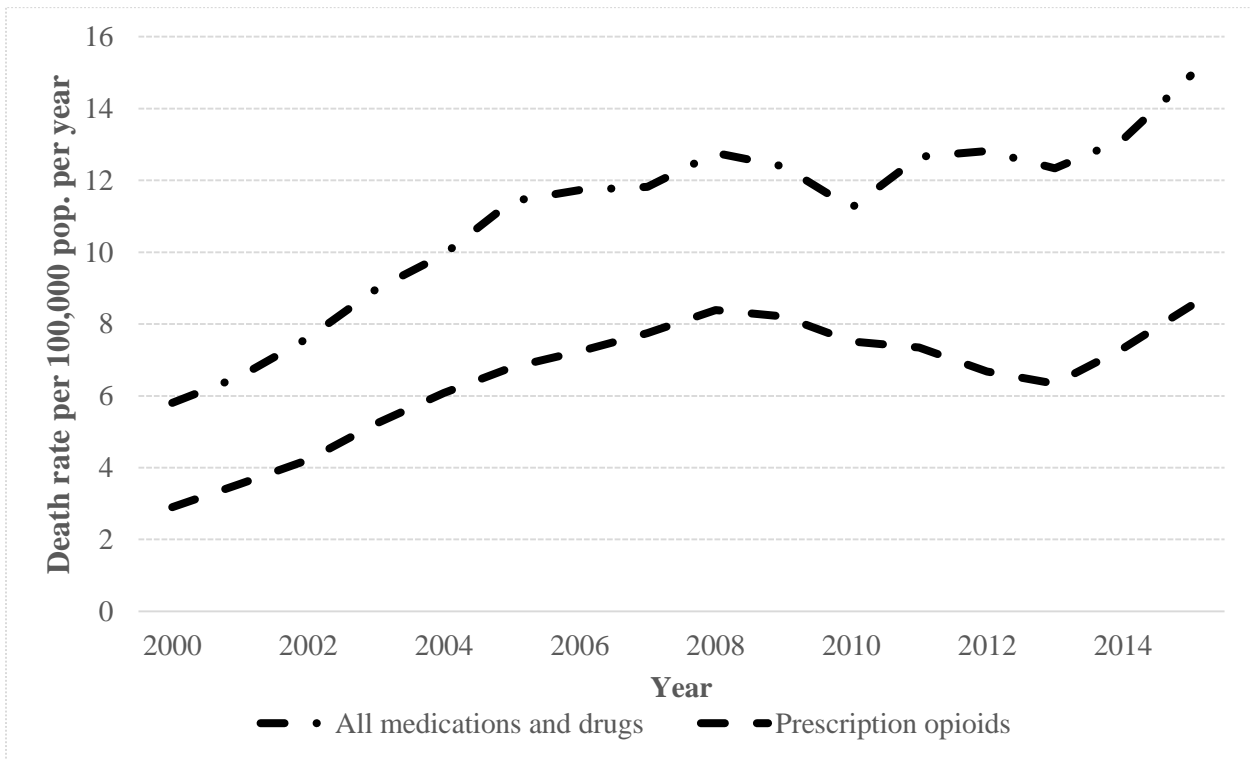
NC now loses nearly 1,500 people each year to drug overdose, the majority of which are related to prescription opioids (n= 854 for the year 2015). Moreover, for each person lost to an overdose in NC, there are an additional nine hospitalizations and 17 ED visits related to drug overdose.[5,6]

Medicaid beneficiaries are a particularly high-risk population for prescription drug misuse, abuse, and overdose. Adults who qualify for Medicaid are generally those with low incomes who have dependents, a disability, or some other specific health care need (e.g., pregnancy).[7] Prescriptions for controlled substances (CS) (i.e., drugs, such as opioids, whose manufacture, possession, or use is regulated by the government because of their potential for abuse), and specifically for opioids, have increased rapidly over the past several years in the Medicaid population. Between 1996 and 2002, opioid dispensing to Medicaid fee-for-service enrollees increased approximately threefold.[8] Additionally, Medicaid beneficiaries are prescribed opioids at roughly twice the rate of non-Medicaid populations, likely due to several factors, including higher rates of disability and chronic disease.[9,10] It also has been suggested that Medicaid beneficiaries may have less access to non-opioid therapies, such as physical therapy, to treat pain-related conditions.[10,11]

A large proportion of the opioids prescribed to Medicaid beneficiaries are linked to potentially inappropriate prescribing.[9] Approximately 40% of Medicaid beneficiaries prescribed opioids in 2010 had at least one indicator of potentially inappropriate use or prescribing, defined as having temporally overlapping opioid and benzodiazepine prescriptions, high daily doses (i.e., prescribed daily dose of $\geq$ 100 morphine milligram equivalents (MMEs)), or long acting/ extended release opioids for acute pain.[12] Serious negative health consequences associated with the disproportionate and high-risk prescribing and dispensing patterns have been identified in this population. Compared to those with other forms of insurance, Medicaid beneficiaries have

both higher opioid-related poisoning hospitalization rates and drug poisoning ED visit rates.[13,14] Analyses from New York, Washington, and Montana indicated that Medicaid beneficiaries have opioid-related death rates three to eight times as high as non-Medicaid beneficiaries.[15-17] In North Carolina specifically, an analyses of 2007 data revealed that Medicaid beneficiaries experienced a third of the unintentional overdose deaths in the state, while representing approximately 20% of the state population.[18]

Several policy interventions have been implemented in an attempt to reduce the negative impacts associated with prescription drug misuse and abuse.[19] Table 1.1 highlights some of the most frequently used strategies with a brief explanation of each strategy's purpose. While some of these strategies are supported by a small evidence base of evaluation-related research, most are lacking empirical support. This type of research is necessary to determine how best to design and apply these strategies in order to optimize public health impact.[19,20]

Table 1.1 Common policies/strategies used to address prescription drug misuse, abuse, diversion, and overdose

Policy/strategy	Purpose
Prescription drug monitoring programs (PDMPs)	State-run electronic databases used to track the prescribing and dispensing of CS. Provides prescribers and pharmacists with important information about patients' CS dispensing history.[21,22]
"Good Samaritan" legislation	Encourages emergency treatment of those experiencing an opioid overdose by providing immunity for low level criminal offenses when a person who is experiencing an overdose or who is present at an overdose calls 911 for assistance or seeks medical attention for themselves or another person.[23]
Naloxone access legislation and naloxone distribution programs	Naloxone is a medication that quickly reverses an opioid-related overdose by neutralizing opioids in a person's system, allowing them to breathe again. Naloxone laws often address criminal, civil, and/or professional immunity from legal action related to the administration of naloxone in an overdose situation.[23,24]

Table 1.1 Common policies/strategies used to address prescription drug misuse, abuse, diversion, and overdose

Policy/strategy	Purpose
Safe disposal/drug "take back" events	Provides a safe, convenient, and responsible means of disposing of prescription drugs.[25]
"Pill mill" legislation	Legislation that often restricts in-office dispensing of CS and/or mandates registration or licensure of pain management clinics, among other requirements.[26]
Provider training and education, including Risk Evaluation and Mitigation Strategy (REMS) materials and prescriber guidelines	The FDA's REMS program requires risk mitigation plans to ensure that benefits of certain prescription drugs outweigh their risks. These can include many different components but often include development of a one-page Medication Guide that is given to a patient when they obtain their opioid prescription at the pharmacy.[27] Prescriber guidelines have been made available at the state level, and the Centers for Disease Control and Prevention (CDC) recently released guidelines at the national level.[28,29]
Improved access to substance abuse treatment, including medication-assisted treatment (MAT)	MAT includes taking a medication (e.g., buprenorphine, methadone) usually once per day to relieve opioid cravings and withdrawal symptoms.[30,31] Many treatment programs also involve a counseling component.
Abuse-deterrent opioid formulations	Drugs designed to minimize the user's ability to physically alter the drug to extract the active ingredient through methods like chewing, crushing, or mixing with a solvent (e.g., alcohol).[32]
Patient review and restriction programs (i.e., "Lock-in" programs)	Programs designed to identify beneficiaries demonstrating potential overutilization of prescription drugs and tightly regulate their access, generally through the requirement that beneficiaries use a single prescriber and/or pharmacy to obtain certain CS for a specified period of time.[33,34]

Of specific interest in this dissertation are "lock-in" programs or patient review and restriction programs. These have generally been used to target specific beneficiary populations, such as the high-risk Medicaid population. Medicaid "lock-in" programs (MLIPs) identify Medicaid beneficiaries demonstrating potential overutilization of prescription drugs and control their access, generally through the requirement that beneficiaries use a single prescriber and/or pharmacy to obtain certain CS for a specified period of time.[33] Because Medicaid legislation has long mandated that states safeguard against unnecessary utilization of services, several states

have operated some version of a "lock-in" program since the 1970s or early 1980s.[35,36] However, with the recent substantial increase in CS misuse, abuse, diversion, and overdose, MLIPs have received a renewed focus in the last several years.[37]

While MLIPs are operational in nearly every state,[33,38] there is wide variation in program design, and limited research on the long-term impacts on beneficiaries. The diversity in MLIP design includes the criteria that trigger enrollment in a state's MLIP, length of time beneficiaries are enrolled in the program, and restrictions placed on beneficiaries while enrolled.[33] While each state has different specific criteria, beneficiaries are generally flagged for enrollment due to filling a certain number of prescriptions and/or visiting a certain number of prescribers and/or pharmacies in a specified period of time (e.g., 30 or 60 days). Additionally, once locked-in, beneficiaries are generally constrained to obtaining CS prescriptions from one prescriber and/or one pharmacy for a 12- to 24-month period. However, as we discuss in detail in Chapter 2, few states have rigorously evaluated the impacts of their MLIPs.

NC's MLIP was implemented in 2010 in response to a Government Accountability Office audit identifying NC as a state with an unusually large number of claims for CS.[39] The MLIP is administered by NC's Division of Medical Assistance (DMA), the division administering Medicaid in NC. Similar to other states, NC's MLIP primarily serves three purposes: 1) to better coordinate care of selected beneficiaries; 2) to reduce diversion of CS; and 3) to reduce expenditures for medically unnecessary prescriptions and health care services needed to treat adverse outcomes from the nonmedical use of CS.[33] NC Medicaid beneficiaries who meet the requirements outlined in Table 1.2 are flagged for potential enrollment in the state's MLIP.[40] If enrolled, beneficiaries are "locked-in" for a 12-month period and restricted to using one prescriber and one pharmacy location to obtain CS prescriptions categorized as opioids

or benzodiazepines, as well as certain anxiolytics (e.g., meprobamate). After 12 months in the program, beneficiaries are released from lock-in requirements, but can become eligible for re-enrollment if criteria for enrollment are again met. (Note: In January 2017, the "lock-in" period in NC changed from a 12- to a 24-month period.[41] This dissertation analyzed data prior to 2017.)

Table 1.2 Criteria for potential inclusion in the NC Medicaid "Lock-In" Program

Controlled substance	Specifications*
Opioid analgesics	>6 claims in 2 consecutive months
Benzodiazepines	>6 claims in 2 consecutive months
Opioid analgesics or benzodiazepines	Obtained from >3 unique prescribers in 2 consecutive months
--	Referred for enrollment by a provider or the NC Division of Medical Assistance

*Note: Cancer patients are generally exempt from consideration for MLIP enrollment.

Few high-quality studies have rigorously evaluated many of the strategies described in Table 1.1, including MLIPs.[20] This dissertation fills important gaps in our understanding of the impacts of MLIPs, and specifically NC's MLIP. Chapter 2 provides a detailed review of the current literature surrounding MLIP impacts, and Chapter 3 outlines the specific aims of this dissertation and gaps in the literature that this dissertation fills.

CHAPTER 2 – LITERATURE REVIEW

2.1 Overview

A review of the literature, searching PubMed, Google Scholar, and ProQuest's Dissertation and Theses databases, was conducted. Because much of the evaluation information on MLIPs is not contained in the peer reviewed literature, but rather involves internal state reports, we also used Google searches to search this "grey" literature. Literature searches included combinations of the following search terms: "Medicaid," "lock in," "opioid," "drug utilization review," "patient review and restriction," "evaluation," "controlled substances," and each of the state names. All searches were initially conducted in November 2015 and repeated in June 2017 to capture any new publications. The reference lists of identified articles were reviewed for additional relevant articles and resources.

This critical review of the literature review is organized in three parts (Sections 2.2-2.4). The first part summarizes what is known about the impacts of MLIPs from various state-based studies, audits, and internal reports (Section 2.2). The second part synthesizes findings from evaluations of lock-in programs implemented by specific managed care organizations (MCOs) (Section 2.3). The third part focuses on initial evaluation results from studies examining impacts of NC's MLIP (Section 2.4). At the end of each section, we provide a summary of the key methodologic limitations of the studies and reports reviewed.

Finally, in Section 2.5, findings from a brief review of studies examining heterogeneity in trajectories and classes of CS use are provided. This review was conducted to inform hypotheses for the second aim of this dissertation.

2.2 Evaluations of MLIPs: State-based (other than NC) Results

This section synthesizes evaluation findings from MLIPs in states other than NC. While nearly every state has a MLIP in place, there is very little rigorous information available on the impacts of these programs. We identified MLIP evaluation results related to healthcare utilization or cost savings from fifteen states; however, most evaluation reports and studies had poorly documented methods and provided a superficial look at program impacts. We first review evaluation results from six states with either peer-reviewed studies of the effects of their MLIPs or with state-based reports or presentations that provided reasonably well documented results. We specifically highlight the year(s) studied in each subheading below to call attention to the fact that results and lessons learned from some of the earlier studies may not be as applicable to the current prescription drug overdose epidemic, which began in the mid-1990s.[42] Additional state-based findings, often from internal state-based reports or audits with very little detail, are briefly summarized in Table 2.1.

Missouri (1976)

The earliest known MLIP evaluation results come from Missouri.[43] In 1977, Singleton published a description of how the state's MLIP operated, as well as the estimated cost savings from the program. In determining which beneficiaries to enroll in the program, Missouri's MLIP staff examined claims looking for three specific areas of overutilization: physician and pharmacy

9

shopping; excessive numbers of prescriptions within thirty, sixty, or ninety days; and the number

of different drugs received vs. the number of physicians prescribing them. Beneficiaries flagged

for potential misutilization were reviewed by a Medicaid physician and/or pharmacist to

determine if the beneficiary's utilization could be justified based on their diagnoses and previous

medical history. If staff determined that the utilization was unjustifiable, a Medicaid caseworker

contacted the beneficiary to discuss the MLIP and explain that they would be "locked-in" to

using one physician and pharmacy. Singleton estimated that the program saved the state between

$1.8 million and $10.95 million in the year 1976 alone and that these savings reduced the state's

Medicaid budget expenditures by at least 2%.[34,43,44]

Hawaii (1980-1983)

Hawaii's MLIP was implemented in 1980 with the following criteria for program

enrollment: (1) engaging in "doctor shopping," defined as consulting multiple providers for the

same reason in a few days, consulting multiple providers specializing in the same area for the

same or different reasons, or consulting providers located in geographically diverse areas for the

same reason; (2) engaging in unnecessary visits for the same reason to the same provider; (3)

using multiple pharmacies to obtain the same drug dispensed by either the same or different

physicians; (4) obtaining excessive doses of CS or drugs with street value; or (5) using

prescription drugs that are inconsistent or inappropriate with a diagnosis (generally, for a long

period of time).[45] Medicaid staff regularly identified beneficiaries meeting misuse criteria, and

Medicaid caseworkers met with beneficiaries to discuss their overutilization. Beneficiaries were

given up to six months to voluntarily address identified issues. If, during this period, Medicaid

staff determined that the issues were resolved, beneficiaries were not formally "locked-in."

However, if misuse appeared to persist, beneficiaries were "locked-in" to using only one primary care provider, pharmacy, clinic, and/or hospital. An evaluation of the MLIP published in 1985 found that from program implementation through 1983, approximately 270 beneficiaries were counseled by caseworkers and 137 restrictive actions were taken. Of those who were counseled, warned, and asked to voluntarily comply, about 21% were no longer overutilizing services one year post-warning. Among those who were enrolled in the MLIP, the degree of abuse was reported to decrease on average while enrolled, and the state was estimated to save more than $900,000 from the program in one year alone.[34,46]

Louisiana (1994-1996)

Louisiana's MLIP was established in the 1970s; however, it was not until the mid-1990s, when Medicaid costs drastically increased, that the MLIP was utilized to a much greater extent with about 2,000 beneficiaries enrolled at any given time. While MLIP beneficiaries could be restricted to one primary care provider, one specialist, and/or one pharmacy, the majority of beneficiaries were only locked-in to one pharmacy. Blake's (1997) dissertation research focused on examining the impact of Louisiana's MLIP on economic and clinical outcomes.[34,35,47] She analyzed claims data for a two year period from mid-1994 to mid-1996 and used t-tests and segmented regression to examine differences in utilization and expenditures one year pre-lock-in vs. the year following lock-in.

Beneficiaries in the MLIP were predominantly female (77%) with a mean age of 48 years and most received disability assistance (74%). Compared to the one-year pre-lock-in period, during lock-in there was an increase in provider continuity (i.e., proportion of services obtained from one provider) and a reduction in the number of inpatient days, as well as in physician visits

and diagnostic tests. Approximately 65% of locked-in beneficiaries filled their prescriptions at a single pharmacy prior to lock-in, as compared to more than 90% during lock-in. Additionally, Blake documented reductions in polypharmacy, use of Schedule II CS, and pharmacy costs. Prior to lock-in, the number of unique prescriptions per recipient per month ranged from 8-10 compared to about 6 after enrollment. Moreover, per recipient adjusted monthly pharmacy expenditures ranged from $300-$400 prior to enrollment compared to $225-$250 after enrollment for those with a physician and pharmacy restriction and about $300 after enrollment for those with only a pharmacy restriction.

Wisconsin (1997)

Potential candidates for Wisconsin's MLIP were identified through both automated surveillance methods and through referral by physicians, pharmacists, and other providers.[48] Candidates with evidence of CS abuse and/or forgery of prescriptions were placed in the state's MLIP and restricted to using a single provider and a single pharmacy for two years. Hladilek et al. (2004) reported that on average, about 130 candidates were reviewed each month, resulting in approximately nine MLIP enrollments per month. Moreover, a 1997 cost-benefit analysis of the program concluded that the MLIP saved $6.16 per dollar spent. This analysis also indicated that the MLIP resulted in a 24% decrease in drug expenditures, 21% decrease in hospitalizations, and a 26% decrease in ED visits.[48]

Washington (2004-2012)

A series of presentations and studies from researchers in Washington have summarized both health care utilization and expenditure changes resulting from their state's MLIP.[28,49-51]

Similar to other states, Medicaid beneficiaries are considered for MLIP enrollment as a result of either a referral from a health care provider or as a result of being flagged in a claims-based analysis that considers numbers of providers visited, prescriptions dispensed, and ED visits, among other factors. MLIP beneficiaries can be locked into using one primary care physician, one pharmacy, one opioid prescriber, one hospital for non-emergency services, or any combination of these for a two-year period. A 2009 analysis revealed that, on average, beneficiaries enrolled in the MLIP had a 37% decrease in physician visits, a 33% decrease in ED visits, and a 24% decrease in the number of prescriptions. Among 518 beneficiaries enrolled in the MLIP in 2006, the average number of opioid prescriptions per beneficiary per month decreased from 3.07 to 1.63, the average number of prescribers decreased from 4.8 to 2.8, and total MMEs decreased from 312 MME/day to 185 MME/day. Savings from the MLIP were estimated at more than $1.5 million per month, and the program was found to save approximately $12 for every $1 invested.

While the state's MLIP demonstrated many positive findings, additional analyses using 2004-2007 data highlighted the fact that MLIP enrollees remained a high-risk population, even after enrollment.[17,45] These analyses indicated that while MLIP enrollees constituted 0.1% of the entire Medicaid population, they accounted for 4.5% of all prescription opioid-related deaths. The annual fatal overdose risk for individuals in the overall state Medicaid population was estimated to be 1 in 6,757, while the estimated risk was 1 in 172 for those enrolled in the MLIP.

Oklahoma (2006)

Oklahoma MLIP beneficiaries were selected for enrollment based on their number of ED visits; number of unique pharmacies visited; number of prescribers/physicians visited; days'

supply of narcotics, anxiolytics, antidepressants obtained; diagnoses of drug dependence; and

number of hospital discharges, among other factors. While enrolled, beneficiaries were "locked-

in" to using one pharmacy. A 2009 analysis of 52 MLIP beneficiaries enrolled from January

2006 through October 2006 found that when compared to the 12 months prior to enrollment,

beneficiaries had less opioid prescription fills, were less likely to visit multiple pharmacies and

physicians, and had fewer ED visits during MLIP enrollment.[45,52] The average number of opioid

prescription fills decreased from 2.16 per beneficiary per month to 1.32, all pharmacy claims

decreased from 4.86 to 3.46, unique pharmacies visited decreased from 2.05 to 0.89, unique

prescribers visited decreased from 2.48 to 1.63, and ED visits decreased from 1.26 to 0.81. In the

first 12 months of MLIP enrollment, per member annual savings were estimated at just over

$600.

In addition to these state-based studies, several internal reports were identified that

provided very brief information on estimates of state MLIP impacts, often in terms of Medicaid

cost savings. These findings are summarized in Table 2.1.

Table 2.1 Brief state-based MLIP evaluation findings

State	Key findings
Colorado[53]	A 2015 state audit report estimated that if Colorado's MLIP, which was not functional at the time of the report, had enrolled just 200 beneficiaries prior to FY 2012, they would have seen a reduction in General Fund expenditures for prescription drugs of $633,725 for FYs 2012 and 2013.
Conneticut[54,55]	The state reported that their drug utilization review activities and MLIP had saved the state $2.4 million in fiscal year 2011 and more than $4 million in fiscal year 2012.
Florida[56,57]	Between October 2002 (when FL's MLIP began) and March 2005, approximately 1,315 beneficiaries were enrolled in the program, which restricts beneficiaries to one provider and/or one pharmacy for up to one year. During that time period, cumulative savings were estimated to be

Table 2.1 Brief state-based MLIP evaluation findings

State	Key findings
	approximately $12.7 million. Several years later, the state's Agency for Health Care Administration reported that due to restrictions set on CS and use of the state's PDMP, which is available to both prescribers and pharmacists, the number of beneficiaries locked-in decreased over time and the number of beneficiaries requiring manual monitoring through the MLIP decreased. As of September 30, 2013, the state reported that there were no longer any beneficiaries in the MLIP.
Iowa[58,59]	Iowa MLIP beneficiaries are restricted to one physician, one pharmacy, and one hospital to obtain prescriptions for a 24-month period. In 2008, the state reported annual cost savings of approximately $2 million, which increased substantially in subsequent years. From July 2010 through September 2012, the state estimated that they had saved approximately $14.8 million in terms of prescription drug and medical care costs.
Kentucky[60]	In 1997, an internal performance audit was carried out on the state's MLIP. Kentucky's MLIP requires enrollees to be restricted to one physician and one pharmacy. The auditors analyzed 170 randomly selected MLIP beneficiaries enrolled between January 1994 and March 1997. They found that average annual claims in the 12 months pre-lock-in were nearly $15,000 and approximately $8,600 in the 12 months following lock-in, for an average estimated savings of $6,400 per beneficiary enrolled.
Louisiana[61]	MLIP beneficiaries in Louisiana are locked-in to using one pharmacy when enrolled. From September 2013 to July 2014, it was estimated that the MLIP saved more than $90,000, or about $15.65 per locked-in beneficiary per month. During this time, the number of beneficiaries locked-in increased from 184 to 884.
Missouri[62]	In Missouri, MLIP beneficiaries can be restricted to a physician, pharmacy, or both. As of October 2015, the state reported 1,485 active MLIP enrollees and a total cost savings, as a result of the MLIP, of more than $550,000 for the year.
South Carolina[63]	South Carolina MLIP beneficiaries are locked into using one pharmacy. At the time of a MLIP review in 2011, the program reported having 199 beneficiaries enrolled. Additionally, since the MLIP started in January 2009, it was estimated that service utilization by beneficiaries in the program decreased 29%. This decrease translated to a total savings of $1.1 million or about $5,581 per MLIP beneficiary.
West Virginia[64]	Beneficiaries enrolled in West Virginia's MLIP are locked-in to one pharmacy for a 12-month period. An analysis of 919 MLIP beneficiaries from September 2011 through June 2012 revealed that the amount paid for CS decreased $48.04 per member per month when comparing the six months pre-lock-in to the first six months during lock-in, yielding an overall savings of more than $264,000 in Medicaid-related drug expenditures.
Wyoming[65]	Wyoming's MLIP was established in 2003. In the first two months of the program, there was an estimated cost savings of nearly $22,000. However,

Table 2.1 Brief state-based MLIP evaluation findings

State	Key findings
	the state reported that over the following year, few additional benefits were observed. They saw no opioid use declines and no significant cost savings to Medicaid during this time.

Summary of Key Limitations

Three key methodologic limitations emerged from the review of evaluations from MLIPs in states other than NC. First, many of the studies reviewed identified cost savings associated with MLIPs. However, these savings may be questionable, since few of the studies used comparison populations of beneficiaries who were not included in MLIPs, and therefore fail to account for decreases that would have occurred even if the beneficiaries had not been enrolled in the MLIP. Second, most studies and reports examined administrative metrics, such as changes in Medicaid-reimbursed dispensed opioids as the endpoint of interest. None of the reviewed studies or reports examined changes in dispensed opioids from other sources of reimbursement, such as personal payment. Third, none of these studies or reports addressed key patient-orientated health endpoints, such as risk of overdose, use of MAT, or use of non-pharmacologic pain management therapies. These limitations leave major gaps in our scientific understanding of the effect of these programs.

2.3 Evaluations of MLIPs: Managed Care Organization (MCO) Results

In addition to studies and reports that took a state-based perspective, we also located evaluation results from six MCOs that examined some form of a lock-in program. In 2005, Beaubien completed a dissertation focused on examining healthcare utilization among MLIP enrollees (n=307) in a Northeastern Medicaid MCO.[66] Analyzing data from January 2000

through October 2002, he found that two-thirds of the MLIP beneficiaries were female and that beneficiaries had a mean age of 46 years (range 17-76 years). The MLIP resulted in a 17% reduction in the number of CS claims, a 9% reduction in the number of medical claims for office visits, and an 11% reduction in the number of medical claims for outpatient hospital visits. Additionally, Beaubien found that while the number of claims for inpatient hospital visits increased 14%, the number for ED visit claims remained approximately stable between pre-lock-in and during lock-in periods.

More recently, Dreyer et al. (2015) conducted an observational cohort study of 59 beneficiaries enrolled in Blue Care Network's (BCN) MLIP from March 2008 through May 2013.[67] BCN is a Medicaid MCO run by Blue Cross Blue Shield of Michigan. BCN beneficiaries were flagged for potential MLIP enrollment quarterly if they had filled more than nine CS prescriptions from more than three prescribers within a three-month period. A committee reviewed flagged beneficiaries, and if enrolled, the review committee contacted the beneficiary's primary care provider to ask him or her to be the beneficiary's sole opioid prescriber. Upon physician agreement, beneficiaries were informed via letter that only CS prescriptions obtained from the one provider would be covered by BCN, and beneficiaries were locked-in to this provider for a 36-month period. Dreyer et al. found that over half (n=32 of 59) of enrolled beneficiaries left the MCO during the study period. In fact, 29% (n=17) of all MLIP-enrolled beneficiaries left within the first six months of enrollment. The attrition rates observed over this time were higher than in the general Medicaid population. The authors also measured changes in appropriate CS use (defined as steady use, decreasing or stopping use, or enrollment in maintenance replacement therapy) and "unstable" use (defined as submitting claims for opioids written by other providers or paying cash for opioids prescribed by other providers) during the

17

study time period. While the percentage of those with appropriate CS use increased, from 31% at

six months to 78% at 36 months, and the percentage with "unstable" use decreased, from 37% at

six months to none at 36 months, the authors acknowledged that selection bias likely contributed

to these results. The authors suggested that beneficiaries who were more likely to continue

unstable or risky opioid use may have been the ones that were also more likely to terminate their

BCN coverage in order to leave the MLIP.

Most recently, in 2014, the Association for Community Affiliated Plans worked with

several MCOs to implement pilot projects aimed at reducing prescription drug abuse in the

Medicaid population.[68] Four MCOs in California, New York, New Jersey, and Ohio chose to

implement MLIPs. Table 2.2 provides key results from these four pilot projects.

Table 2.2 Association for Community Affiliated Plan's pilot projects involving implementation of MLIPs in MCOs

MCO	MLIP pilot project specifics	Results	Strengths/Limitations
• Affinity Medicaid MCO, based in New York (NY), is one of the largest Medicaid MCO programs in the NY metro area. • 6 provider sites with a total of 10-15 prescribers and about 250 beneficiaries participated in the pilot project.	• MLIP beneficiaries received written notice of enrollment in the program, as did the NY State Medicaid office. • During initial visits with MLIP-enrolled beneficiaries, participating pain management specialists conducted risk assessments and pain screenings. • MLIP beneficiaries signed pain contracts and were required to undergo random testing to check for	• Pain management specialists reported an increased ability to retain beneficiaries who previously would have been discharged from care due to difficulties with adherence to pain contracts. • Costs for CS prescriptions declined 18% among MLIP beneficiaries. • No beneficiaries received opioid	• Strength: multiple layers of MLIP beneficiary support. • Limitation: high beneficiary turnover. Because Medicaid beneficiaries were allowed to change health plans every month, addressing addiction problems was challenging. However, when a beneficiary who had been enrolled in a MLIP changed health plans, the new plan was informed of their lock-in status.

18

Table 2.2 Association for Community Affiliated Plan's pilot projects involving implementation of MLIPs in MCOs

MCO	MLIP pilot project specifics	Results	Strengths/Limitations
	use of drugs and doses beyond those prescribed. • Beneficiaries were required to remain under one designated prescriber's care in order to obtain CS prescriptions.	prescriptions in combination with buprenorphine or benzodiazepines (high-risk combinations). • Average morphine equivalent dose declined 31 mg.	• Limitation: lack of pain medicine specialists in NY (pain medicine specialists administered this pilot project). Shortage could limit future program dissemination.
• CalOptima based in Orange County, California, operates a health care network called Monarch HealthCare, which piloted the MLIP	• Pharmacy staff identified beneficiaries who exhibited drug-seeking behavior and referred them for enrollment. • Enrolled beneficiaries were assigned to pain management specialists and were required to sign pain management contracts to indicate consent with the MLIP and commitment to comply with requirements.	• Among 87 MLIP beneficiaries, there was a 50% reduction in the average number of opioid prescriptions obtained per beneficiary per month (from 3.6 to 1.8) and a 32% reduction in the average number of opioid prescriber groups visited per beneficiary (from 2.5 to 0.8).	• Limitation: beneficiaries who changed health care networks or who lost eligibility for Medicaid were disenrolled from the MLIP.
• Horizon New Jersey Health (backed by Horizon Blue Cross Blue Shield of NJ) enrolled 171 beneficiaries in their MLIP pilot by the end of 2014.	• Pilot included support services for beneficiaries, pharmacies, and prescribers. • Beneficiaries were enrolled based on prescription histories. Notification letters were sent to enrolled members, their primary care provider,	• Physicians provided positive feedback about notification letters. • Preliminary analyses on MLIP-enrolled beneficiaries found reductions in the number of CS dispensed per member, spending	• Strength: program integration in a managed care model. Recognizing that MLIP beneficiaries often have a range of unmet health and quality of life-related needs, when case managers contacted MLIP-enrolled beneficiaries to inquire about their pain management care and

Table 2.2 Association for Community Affiliated Plan's pilot projects involving implementation of MLIPs in MCOs

MCO	MLIP pilot project specifics	Results	Strengths/Limitations
	and pharmacy they were locked-in to. • When a MLIP beneficiary filled two or more prescriptions from two or more prescribers for CS within the same therapeutic class, the prescriber was sent a notification letter asking if they were aware and whether they would consider modifying the beneficiary's medication in light of the information. • Physicians encouraged to discuss treatment plans with beneficiaries and each other.	per CS claim, and the number of pharmacies used.	appointments, they also evaluated beneficiaries' needs for critical resources (e.g., food, transportation, housing).
• CareSource, a nonprofit managed health care plan headquartered in Dayton, Ohio • Largest Medicaid managed health care plan in Ohio and second largest in US. • 270 beneficiaries enrolled in	• Beneficiaries who obtained prescriptions from multiple pharmacies and prescribers were enrolled in the MLIP. • Program included a pharmacy lock-in restriction with a case management "wraparound." • Beneficiaries received letters informing them that they had to fill all prescriptions at one pharmacy and have	• Program administrators acknowledged that many MLIP-enrolled beneficiaries paid cash for prescriptions to avoid lock-in and bypass the MLIP approval process. They reported that they were trying to find effective ways to address this issue.	• Strength: case management "wraparound" component connected beneficiaries with community resources, social services, and health care professionals. • Case managers were trained in effective communication and listening strategies and worked to build long-term, supportive relationships with beneficiaries. Worked to help beneficiaries

Table 2.2 Association for Community Affiliated Plan's pilot projects involving implementation of MLIPs in MCOs

MCO	MLIP pilot project specifics	Results	Strengths/Limitations
their pilot MLIP.	medical services coordinated by their primary care provider. • Beneficiaries were generally locked-in for 18 months.		acknowledge potential substance abuse and engage in treatment.

Summary of Key Limitations

Similar to the studies reviewed in Section 2.2, key methodologic limitations included lack of comparison populations. As noted above, without such a group, differences due to MLIP enrollment and differences due to other causes (e.g., changing prescribing trends) could not be disentangled. Additionally, the evaluations reviewed in this section, again, failed to examine key patient-oriented health endpoints (e.g., use of MAT, overdose). Finally, while two evaluations considered beneficiary acquisition of CS using non-Medicaid payment sources (e.g., out-of-pocket payment),[67,68] these evaluations were limited to either anecdotal reports or small samples with large losses to follow-up, preventing rigorous examination of this issue.

2.4 Evaluations of MLIPs: North Carolina Results

High CS utilization and associated negative consequences among NC Medicaid beneficiaries prompted the establishment of the NC MLIP. In fiscal year 2010 alone, approximately 273,000 Medicaid beneficiaries filled a prescription for at least one opioid, and opioid claims cost NC Medicaid about $48 million.[69] Additionally, 170,000 beneficiaries filled a prescription for at least one benzodiazepine, and Medicaid spent $16 million on benzodiazepine claims. At the time of NC's MLIP establishment in 2010, the state identified about 3,000

beneficiaries meeting criteria for MLIP enrollment due to potentially inappropriate or high-risk CS use, as determined by the state's MLIP enrollment criteria (see Table 1.2). However, due to resource constraints, only about 200 beneficiaries were enrolled each month.

In March 2011, around 950 of 3,000 eligible NC Medicaid beneficiaries were reported to be "locked-in."[70] Early evaluation analyses indicated that the MLIP resulted in fewer prescription claims, as well as fewer visits to hospitals, clinics, physician offices and EDs. The reduction in resource utilization translated to a total cost savings of approximately $4,620 per locked-in beneficiary per year.[70] In May 2012, the NC Department of Health and Human Services (DHHS) issued a press release on initial MLIP impacts.[71] They found that nearly 2,500 beneficiaries had been enrolled in the program, and when prescription claims for the three months before MLIP enrollment were compared to claims for the three months after enrollment, they found that beneficiaries received 2.3 million fewer opioid pills, or approximately 1,000 fewer pills per beneficiary. Additionally, MLIP beneficiaries had fewer hospital, ED, and dental visits and underwent fewer radiology scans and lab tests after enrollment in the program. Lastly, the NC DHHS estimated that more than $5.2 million in medical and pharmacy claim costs were saved in the first year of MLIP operation alone.[71]

Similar to MLIP evaluation findings from other states, these early NC specific analyses indicated positive impacts in the form of cost reductions, as well as reductions in medical and pharmacy utilization measures.[43,46,47,49,57,59,72,73] However, much of this previous literature, including the preliminary NC analyses, lacked critical information on all CS dispensed to MLIP beneficiaries, as they only examined CS prescriptions reimbursed by Medicaid.[43,46,47,49,57,59,72,73] To address this issue in NC, Skinner et al. were awarded CDC grant #U01 CE002160-01 to establish a unique, linked database, allowing for comprehensive examination of Medicaid

beneficiaries' dispensed CS prescriptions.[74] This database linked NC Medicaid Claims data from October 2008 through June 2013 to data from NC's Controlled Substances Reporting System (CSRS) from October 2009 through June 2013 for beneficiaries enrolled in NC's MLIP.[26,27] NC's CSRS is a rich database that provides detailed information on each CS dispensed in the state through the aggregation of patient, provider, prescription, and pharmacy data, regardless of source of payment.[75]

The primary aims of this project were focused on gaining a better understanding of how the NC MLIP operates through stakeholder (i.e., pharmacist) interviews and understanding changes in beneficiaries' prescription dispensing behaviors while enrolled in the MLIP, as compared to periods prior to MLIP enrollment.[74] Overall, findings from this project suggested that paying out-of-pocket for CS prescriptions, and not filing with Medicaid, was not a rare practice among MLIP beneficiaries and that integration of this information in MLIP evaluations had the potential to substantially affect our understanding of MLIP impacts.[76-78] Below we summarize additional key findings from this project, as well as findings from a UNC dissertation recently completed by Andrew Roberts,[79] who also made use of this unique database.

Using Medicaid claims only, Skinner et al. (2015) first set out to determine the effect of the NC MLIP on the number, characteristics, and cost of opioid prescriptions received by beneficiaries.[76,80] Claims data from October 2008 through June 2013 were analyzed on beneficiaries who were ever enrolled in the MLIP (n=6,148). Compared to pre-enrollment, they found that during MLIP enrollment, beneficiaries had fewer opioid prescriptions on average each month (1.6 vs. 0.8), visited fewer pharmacies to obtain opioid prescriptions per month (1.0 vs. 0.5), and had a reduced days' supply of opioids per month (23.4 vs. 19.5). Additionally, using maximum likelihood mixed effects models with an autoregressive residual error structure and

controlling for race/ethnicity, sex, age, and living arrangement, they found that enrollment in the MLIP resulted in a lower odds of having any opioid prescription.

Building from these analyses, the study team then went on to examine how enrollment in the MLIP might affect circumvention of opioid prescriptions.[77,81] Circumvention was defined as paying cash for one's opioid prescriptions, instead of using the Medicaid payment system. To identify cases of circumvention, Skinner et al. looked for records of Medicaid beneficiaries' dispensed prescriptions in the CSRS for which there was no corresponding Medicaid claim. They analyzed 4,352 people who were enrolled in the MLIP at some point during the first two years of the program (i.e., from October 2010 through September 2012). Using maximum likelihood mixed effects models with an autoregressive residual error structure and controlling for several demographic variables, they found that enrollment in the MLIP was associated with an increased odds of prescription circumvention. The odds of having a circumvented prescription per beneficiary per month while enrolled in the MLIP was about 5 times the odds of having one prior to MLIP enrollment. Additionally, they found when compared to the pre-enrollment period, during enrollment in the MLIP, about 0.58 more prescriptions per beneficiary per month were circumvented, 23 additional pills per beneficiary per month were circumvented, and about 0.47 additional prescribers per beneficiary per month were used in obtaining circumvented prescriptions.

Finally, to supplement findings from these quantitative analyses, qualitative data collection and analyses were carried out to gain a better understanding of provider perceptions of the MLIP and of overall program operation. Structured qualitative interviews were conducted with twelve NC pharmacists. Overall, pharmacists reported a positive experience with the MLIP; however, they generally expressed skepticism regarding its larger impact on substance misuse

and abuse in the state.[82] Additionally, pharmacists identified several areas needing improvement with respect to MLIP operation, including improved communication by the DMA as to the MLIP's purpose and specific operating procedures, as well as improved procedures to allow beneficiaries to see multiple prescribers in the same practice and multiple physicians to assist with complex health problems.

To extend the work of the original project, Roberts' dissertation focused on exploring the characteristics of both beneficiaries who circumvented the MLIP, as well as characteristics of the prescriptions that were circumvented.[78,79,83] Roberts constructed a cohort of beneficiaries enrolled in the MLIP at some point between October 1, 2010 and March 31, 2012. To be included in the cohort, beneficiaries were required to be continuously enrolled in Medicaid from October 1, 2009 through a minimum of six months after their entry into the MLIP. Using general estimating equations, he found that MLIP enrollment was associated with a four-fold increase in the rate of obtaining circumvented CS per beneficiary per month. Additionally, he found that having circumvented CS fills was more common among MLIP beneficiaries who were younger, who lived in areas with high supplies of dispensing pharmacies, who had an anxiety disorder diagnoses, and who had a high physical comorbidity burden, as measured by the Charlson co-morbidity score. Roberts also completed a prescription-level analysis to examine whether certain opioids were targeted more often for circumvention after enrollment in the MLIP. He found that "riskier" prescriptions (i.e., long-acting opioids, Schedule II opioids, and higher average daily doses of opioids) were not obtained more often by circumvention after MLIP enrollment. In fact, he found that for opioids obtained through circumvention, the likelihood that they were a long-acting product declined after MLIP enrollment, as did the average daily dose. Roberts suggested that this might have been due to cost, as many of these high-risk prescriptions may have been too

cost prohibitive to pay for out-of-pocket. He concluded that although MLIP enrollment caused beneficiaries to engage in circumvention more often, the risk profile of the specific drugs circumvented did not appear to increase.

Summary of Key Limitations

While initial research evaluating NC's MLIP improved on key limitations from previous evaluations (e.g., consideration of all CS prescriptions dispensed to beneficiaries, as opposed to just Medicaid-reimbursed CS prescriptions), gaps remain in our understanding of NC MLIP effects. Specifically, improvement in disentangling MLIP effects from secular trend effects is one potential area for methodologic advancement. Other developments could include consideration of a larger range of patient-oriented health endpoints (e.g., use of MAT, overdose) and examination of effects over longer time periods (i.e., both immediate and sustained effects).

2.5 Key findings from Studies Examining CS Use Classes and Trajectories

Finally, to inform hypotheses for the second aim of this dissertation, this section provides a brief review of studies examining heterogeneity in trajectories and classes of CS use.

Research has demonstrated that substance use trajectories and types of users are often heterogeneous across populations, but there has been no research on whether and how substance use trajectories might differ for different types of beneficiaries both while enrolled in the MLIP and following release from the program.[84-91] To inform hypotheses of how trajectories might differ for beneficiaries enrolled in the MLIP over time, a brief literature review on heterogeneity in CS use trajectories for other populations (i.e., not MLIP-enrolled populations) and classes of CS users was conducted. Findings from this review are briefly summarized below.

Research examining trajectories of benzodiazepine use among adolescents identified four distinct types of users: occasional, decelerating, accelerating, and chronic users.[86] Factors predicting the accelerating or chronic trajectories included having a history of psychosis or epilepsy, having benzodiazepine prescriptions provided by physicians from multiple specialties, and taking benzodiazepine medications with a long half-life. Additionally, research on trajectories of drug use—including cocaine, opioid, and/or amphetamine use—identified non-user, early occasional users, persistent occasional users, and early frequent/later occasional user types.[87] Several characteristics were predictive of continued drug use over time, including demographic characteristics (i.e., black men) and social characteristics (e.g., whether the family of origin was characterized by abuse/neglect and parental substance use).

Using cross-sectional study designs, researchers have also examined typologies of prescription opioid users in various populations. One study of a large sample of adults assessed for substance abuse treatment found that opioid users were best grouped as: using as prescribed, prescribed misusers, medically healthy abusers, and illicit users.[91] The different strata of users varied according to race/ethnicity, gender, concurrent substance abuse, duration of prescription opioid abuse, mental health problems, and addiction severity index scores. Another study examined chronic opioid users in a large health maintenance organization in Washington State.[90] They identified three types of chronic opioid users: a "typical" group, in which beneficiaries tended to have persistent, moderate mental health and pain symptoms; an "addictive behaviors" group, in which beneficiaries tended to have elevated mental health symptoms and opioid problems but pain symptoms similar to the "typical" group; and a "pain dysfunction" group with significantly higher pain interference as well as elevated mental health and opioid problems.

Prescribed average daily doses of opioids were three times higher for those in the two latter groups and was strongly associated with class membership after adjusting for other variables.

2.6 Summary

Little information is available on MLIP impacts on beneficiaries' healthcare utilization and health outcomes; studies have largely examined cost savings to Medicaid. While MLIPs appear to be a promising approach that may reduce prescription drug misuse, abuse, and diversion, there is much we do not know about their impacts on beneficiaries enrolled.[20] Studies have documented Medicaid-related cost reductions associated with MLIP implementation, as well as reductions in certain medical and pharmacy utilization measures. [35,43,46-52,54,55,57,59-67,69-73] However, these studies have lacked potentially critical information on all CS dispensed to MLIP beneficiaries by only examining CS prescriptions reimbursed by Medicaid. [35,43,46-52,54,55,57,59-67,69-73] Moreover, studies have failed to examine patient-orientated health endpoints, such as risk of overdose or use of MAT.

The novel, linked NC Medicaid claims-CSRS database provided by the Skinner et al. grant (i.e., the parent study for this dissertation) is among the first of its kind and provides a more complete understanding of Medicaid beneficiaries' dispensed CS prescriptions.[74] While initial analyses by the parent study team and Roberts et al. have provided important insights concerning the impact of MLIP enrollment on CS prescription fills while enrolled,[76-80,83] additional gaps persist in understanding the sustained and differential impacts of the NC MLIP. Given that these programs affect thousands of beneficiaries on an annual basis, there is a pressing need to address key gaps in the evidence base. Chapter 3 outlines the specific aims of this dissertation and key gaps filled.

CHAPTER 3 – SPECIFIC AIMS

In this dissertation, we examined the impact of the NC MLIP on numbers of dispensed CS prescriptions and the dosages of opioids dispensed following release from the MLIP, providing important information on the sustained impacts of the program. Understanding whether beneficiaries' CS prescription fills and opioid dosages decreased, increased, or returned to similar levels following release from the MLIP, as compared to prior to MLIP enrollment, provides important information on larger program impacts. Moreover, comparing CS dispensing and opioid dosages following release from the MLIP to during MLIP-enrolled periods allowed us to examine the extent to which program impacts (i.e., overall reductions in dispensed CS prescriptions but increased out-of-pocket payments) were sustained or attenuated following release from the MLIP.

Additionally, we examined whether trajectories of beneficiaries' dispensed opioid dosages differed across MLIP-related periods (i.e., prior to, during, and following release from the MLIP) for different strata of the beneficiary population. Our study was designed to extend previous work on underlying heterogeneity within populations of substance users and was the first to investigate potential heterogeneity of opioid dosage trajectories in a MLIP population. Findings from our trajectory analyses can be used to provide information that may help further focus the design of the MLIP by detecting attributes of beneficiaries who might need additional targeted intervention, such as increased case management services, complementary or alternative treatment approaches (e.g., physical therapy), and screening for medication-assisted therapy.

Aim 1: **Assess the impact of exposure to the NC MLIP on numbers of dispensed CS prescriptions and the dosages of opioids dispensed in the year following release from the MLIP**. Using generalized estimating equations (GEE) to account for within-individual correlation over time, we examined numbers of dispensed CS prescriptions and dosages of opioids dispensed in the 12-month period following release from the MLIP, compared to a pre-MLIP period. We also estimated measures of association comparing the during MLIP enrollment period to a pre-MLIP period. While we expected that the MLIP had different impacts for different types of beneficiaries across program periods (e.g., no change in CS use for some, decreased use for others), we hypothesized that we would observe the following average impacts described below.

Hypothesis 1a: On average, the number of CS prescriptions reimbursed by Medicaid and the dosage of opioids obtained from Medicaid-reimbursed prescriptions would be lower following release from the MLIP than prior to enrollment, but greater than during MLIP enrollment.

Hypothesis 1b: On average, the number of CS prescriptions not reimbursed by Medicaid and the dosage of opioids obtained from non-reimbursed prescriptions would be greater following release from the MLIP than prior to enrollment, but lower than during MLIP enrollment.
Rationale: Analyses from the parent study suggested that some MLIP beneficiaries obtained some opioid and benzodiazepine prescriptions through out-of-pocket payments while in the MLIP; the extent to which this behavior persisted following release from the MLIP was unknown.

30

Aim 2: Examine heterogeneity in beneficiaries' trajectories of dispensed opioid dosages across periods prior to, during, and following release from the MLIP. Using latent class growth analyses, we estimated average opioid dosage trajectories across MLIP-related periods in order to approximate the underlying distribution of trajectories across the MLIP-enrolled beneficiary population. We quantified and described detected patterns of longitudinal change, as well as the attributes of beneficiaries that were best captured by different trajectories.

Hypothesis: At least three trajectories of dispensed opioid dosages would be identified: a trajectory that quickly declined during MLIP enrollment and remained low and stable, even post-MLIP; a trajectory that remained at a high but steady level across program periods with little change at program enrollment or disenrollment; and a trajectory that declined during MLIP enrollment and increased post-MLIP, however not to the same level as pre-MLIP. These trajectories were hypothesized to differ according to the following covariates: age, comorbidity burden, and recent history of mental health disorders, pain conditions, and substance use disorders.

Table 3. Overview of Dissertation Aims

	Objective	Data	Analysis Overview
Overall	To examine sustained impacts of a MLIP and to gain a detailed understanding of heterogeneity in dispensed opioid dosages across periods prior to, during, and following release from the MLIP.	Linked NC Medicaid claims-NC CSRS records (i.e., PDMP data) was used for the period of 10/1/2009 through 6/30/2013 (3.75 years of data). Data included persons enrolled in the MLIP at some point between 10/1/2010 (when the program started) through 9/30/2012.	Observational prospective cohort study design used. See cohort definitions below.
Aim 1 (Chapter 6)	Assess the impact of exposure to the NC MLIP on numbers of dispensed CS prescriptions and the dosages of opioids dispensed in the year following release from the MLIP.	Exposure: 12 months in the MLIP Outcomes: number of opioid and benzodiazepine prescriptions dispensed per person per month (total #, # reimbursed by Medicaid, # not reimbursed by Medicaid); average daily dosage of opioids dispensed per person (in terms of average daily morphine milligram equivalents (MMEs)) (overall amount, amount obtained from Medicaid-reimbursed prescriptions, amount obtained from prescriptions not reimbursed by Medicaid) Covariates: age, sex, race, urbanicity of the beneficiary's county of residence, overdose death rate in the beneficiary's county of residence, Medicaid aid category, Medicaid class code, history of alcohol or other substance use-related disorders, history of medication-assisted treatment for opioid addiction, history of an overdose event, number of unique pharmacies visited, number of emergency department visits, number of inpatient admissions, history of	Cohort: independent living adults (e.g., excluded those living in skilled nursing facilities) between the ages of 18 and 64 years who were enrolled in the NC MLIP between October 2010 and September 2012. Followed from the first day of receiving any CS prescription (for outcome of CS dispensed) or opioid prescription (for outcome of MMEs dispensed) on or after October 1, 2009, throughout their period of lock-in, and up to one year following program release or until June 30, 2013, whichever came first. To avoid conflating program effects for those who remained continuously enrolled in the MLIP and those who exited the MLIP prior to completion, analyses were restricted to those who remained in the MLIP for a full 12 months or were administratively censored in June 2013, the last month for which we had data. Outcome measures (listed to the left) following MLIP

		specific pain-related diagnoses (e.g., arthritis, back, neck, headache/migraine, fibromyalgia, sickle cell), history of specific mental health-related diagnoses (e.g., depression, anxiety, bipolar, schizophrenia), Charlson comorbidity index, and temporal trend measures.	release and during MLIP enrollment were compared to those in a pre-MLIP enrollment period GEE were used to provide estimates of measures of association (e.g., count differences, count ratios).
Aim 2 (Chapter 7)	Examine heterogeneity in beneficiaries' trajectories of dispensed opioid dosages across periods prior to, during, and following release from the MLIP.	To examine dispensed opioid dosages, we calculated average daily MMEs of dispensed opioids (paid for using any payment source). For modeling purposes, we averaged each beneficiary's average daily MMEs across each calendar month. We then log transformed this monthly average to obtain an approximately normal distribution for improved model estimation. Trajectories were estimated across months prior to, during, and following release from the MLIP. Latent classes were characterized by the covariates described above in Aim 1.	Cohort same as above (i.e., followed from first day of receiving any opioid prescription on or after October 1, 2009, throughout their period of lock-in, and up to one year following program release or until June 30, 2013, whichever came first. Followed only those who remained in the MLIP for a full 12 months or were administratively censored in June 2013, the last month for which we had data). Latent class growth analysis was used to disentangle and describe the number and shape of different trajectories of dispensed opioid dosages across periods prior to, during, and following release from the MLIP, as well as to characterize trajectory groups by important covariates.

In Chapter 4, we provide an overview of the methods used to fulfill these aims.

Additional details about the methods, as well as results and discussion of results can be found in

Chapters 5-7.

To construct an appropriate cohort for Aim 1 and Aim 2 analyses, we conducted a

detailed analysis of those eligible for, enrolled in, and retained in the NC MLIP. Chapter 5 is the

result of that analysis and was essential to informing cohort inclusion/exclusion criteria for Aim

1 and Aim 2 analyses (Chapters 6 and 7, respectively).

CHAPTER 4 – METHODS

4.1 Overview

In this dissertation, we applied advanced modeling methods to gain insight into the sustained impacts of NC's MLIP and to explore heterogeneity in trajectories of dosages (MMEs) of opioids dispensed across periods prior to, during, and following release from the MLIP. To accomplish these aims, we utilized linked data that provided a comprehensive picture of dispensed CS acquired by beneficiaries.[74] This data set allowed for more valid estimation of a MLIP's impacts by accounting for all CS dispensed, data which other studies have lacked.[35,43,46-52,54,55,57,59-67,69-73] Capturing information on all CS prescriptions dispensed, including those not submitted for Medicaid reimbursement, allowed us to understand how prescription dispensing is truly changing over time, as compared to how dispensing might appear to be changing in Medicaid claims. Analyses from the parent study indicated that paying for prescriptions out-of-pocket, as opposed to filing with Medicaid, was not a rare practice among NC MLIP beneficiaries, and therefore, having information on prescriptions filled by all payment methods, as compared to only those paid for by Medicaid, can notably change our understanding of MLIP impacts.[76-79,83]

Additionally, the large and multi-year nature of this data set allowed us to examine sustained impacts. This was the first study to examine the sustained impacts of a MLIP in the months following disenrollment, contributing important information about the larger influence of the program.

Finally, our study used an advanced analytic method, latent class growth analysis (LCGA), to model and explore heterogeneity in beneficiaries' dosages of opioids dispensed across MLIP-related periods. Latent class growth analysis has become an increasingly popular exploratory tool that can be used to approximate and describe different patterns of change within a larger population.[92-98] While the approach has been successfully used to understand longitudinal change in other substance use-related behaviors for different subpopulations,[85-91,99,100] it has never been used to examine different patterns of change associated with MLIP enrollment. Identification of different patterns of longitudinal change and the types of beneficiaries that tend to follow these trajectories can help inform future MLIP improvements.

4.2 Data Sources

In this section, we describe the two databases linked by the parent study (i.e., the CSRS and Medicaid claims), the linking process, and the final dataset available for analysis, including how beneficiaries were enrolled in the MLIP and therefore our analytic dataset. As previously mentioned, the parent study linked NC Medicaid claims to records from NC's CSRS from October 2009 through June 2013 for all beneficiaries enrolled in NC's MLIP at some point between October 2010 and September 2012.[74]

4.2.1 Controlled Substances Reporting System (CSRS)

NC's CSRS is a rich database that provides detailed information on each CS dispensed in the state through the aggregation of patient, provider, prescription, and pharmacy data.[75] The NC legislature gave authority for the establishment of the CSRS in late 2005 through passage of the NC CSRS Act (NCGS 90-113.70).[101] Under this Act, the purpose of the CSRS was defined as

follows: "to improve the State's ability to identify controlled substance abusers or misusers and refer them for treatment, and to identify and stop diversion of prescription drugs in an efficient and cost-effective manner that will not impede the appropriate medical utilization of licit controlled substances." Additionally, under this Act, the Drug Control Unit in the Division of Mental Health, Developmental Disabilities, and Substance Abuse Services in the NC DHHS was given the responsibility of administering the CSRS. The CSRS began operation on July 1, 2007, and all pharmacies dispensing CS (schedules II-V) in NC began reporting to the system monthly.[102] On August 1, 2008 pharmacy reporting increased to bimonthly, and as of, January 2, 2012, all pharmacies were required to report weekly. Prescribers and dispensers of CS are able to access information on CS to assist and help guide in the care of their patients.[103] The following information is captured in the CSRS: unique identifiers for prescribers, dispensers, and patients; location (county-level) for dispensers and patients; the prescription's quantity, days' supply, indication of a new fill or refill, National Drug Code (NDC), and date prescribed and dispensed; and the age and gender of the beneficiary. While the CSRS has recently started collecting information on the method of payment for each CS dispensed, this information was not available for this study.

4.2.2 Medicaid Claims

In 2015, 18% of the NC population was covered by Medicaid.[104] Medicaid benefits were available to the following major groups of NC residents: 1) those who were pregnant and had household incomes up to about 200% of the federal poverty level; 2) parents with dependent children and household incomes up to about 45% of the federal poverty level (e.g., for a family of three, income cannot exceed $667/month); 3) blind persons with incomes below the poverty

limit; 4) persons under the age of 65 years who were unable to work due to a severe disability that was expected to last at least 12 months and had incomes below the poverty limit; 5) persons aged 65 years or older with incomes below the poverty limit; 6) certain adults with long-term care needs (e.g., nursing care for older adults, others with long-term disabilities); and 7) children whose caregivers' incomes fell below 133% or 210% of the poverty limit, depending on the child's age.[7] Those in the latter three groups were not included in our analyses (see Section 4.3).

NC Medicaid claims data were obtained from the DMA's Data Retrieval Information and Validation Engine (DRIVE).[105] DRIVE is a Medicaid data warehouse that contains Medicaid eligibility information, prior authorization data, drug data, and other reference information. DRIVE is updated weekly, pulling information from the Medicaid Management Information System (MMIS), which processes claims for Medicaid.[106] Data available through DRIVE includes beneficiary demographic information, beneficiaries' periods of enrollment, and adjudicated pharmacy and medical claims. Additionally, information on enrollment in the MLIP is recorded in DRIVE.

4.2.3 Linkage and Final Database

To link the DRIVE data to the CSRS data, the parent study hired a programmer external to the study. Manual linkage was performed using a standardized protocol that included deterministically matching records based on the first five letters of the beneficiary's last name, date of birth within six months, and the first two or three letters of the beneficiary's first name. The protocol included rigorous data integrity checks and steps to help ensure that all of a given beneficiary's records were linked and that issues such as minor misspellings or use of a common

nickname would not prevent linkage. Once linked, dummy identifiers were assigned to all beneficiaries and identifying information was deleted prior to delivery to parent study staff.

The final linked data set contains comprehensive information on Medicaid beneficiaries enrolled in the MLIP at some point between October 2010 and September 2012, including all claims data and information on all CS dispensed to these beneficiaries, at any point from October 2009 through June 2013. Beneficiaries were enrolled in the MLIP on a monthly basis. While approximately 3,000 Medicaid beneficiaries were initially eligible for MLIP enrollment, the DMA only enrolled approximately 200 beneficiaries per month, due to resource constraints.[69,107] Eligibility for the program was determined each month by a vendor who contracted with Medicaid. The vendor examined the prescription dispensing history of all Medicaid beneficiaries for the previous two months and determined which beneficiaries met the eligibility criteria outlined in Table 1.2 (i.e., based on number of prescriptions obtained and prescribers visited). From those eligible, beneficiaries were then ranked and selected for enrollment using a proprietary beneficiary review algorithm that factored in the number of prescriptions obtained, quantity received, days' supply received, paid amounts, and distinct prescribers and pharmacies visited, combined with a clinical review process by pharmacists employed by the vendor. The vendor submitted its selected list of 200 beneficiaries each month to the DMA, and upon approval by the DMA, the vendor then sent each beneficiary a letter notifying them of their enrollment in the program. Enrolled beneficiaries were restricted to using one prescriber and one pharmacy location to obtain prescriptions categorized as opioids, benzodiazepines, or certain anxiolytics for a 12-month period. Beneficiaries were given 30 days to choose and nominate a preferred prescriber and pharmacy before restrictions began. If they did not respond to the DMA with their preferred prescriber and pharmacy, they were assigned one of each.

4.3 Study Design

Study designs for Aims 1 and 2 are discussed in the "Methods" subsections of Chapters 6 and 7, respectively. We briefly summarize study designs for Aims 1 and 2 here.

For Aim 1 (Chapter 6), we used an observational prospective cohort study design. We established and followed a cohort of independent living adults (e.g., excluded those living in skilled nursing facilities) between the ages of 18 and 64 years who were enrolled in the NC MLIP between October 2010 and September 2012. We estimated program effects while locked-in and following MLIP release on numbers of dispensed CS per person-month and the dosage (average daily MMEs) of dispensed opioids per person, as compared to a period prior to MLIP enrollment.

When examining MLIP impacts on dispensed CS, beneficiaries in our cohort were followed from the first day of receiving any CS prescription (i.e., opioid or benzodiazepine) on or after October 1, 2009, throughout their period of lock-in, and up to one year following program release or until June 30, 2013, whichever came first. When examining MLIP impacts on dosages (average daily MMEs) of dispensed prescription opioids per person, beneficiaries were followed in the same manner, except that their start of follow-up was the first day of receiving any opioid prescription, as opposed to any opioid or benzodiazepine prescription.

To avoid conflating program effects for those who remained continuously enrolled in the MLIP and those who exited the MLIP prior to completion (see Chapter 5), we restricted the analysis to those who remained in the MLIP for a full 12 months or were administratively censored in June 2013, the last month for which we had data. We defined continuous enrollment

as no more than a 7-day gap in coverage. These beneficiaries constituted 62% of all beneficiaries ages 18-64 years with an independent living arrangement who were ever enrolled in the MLIP between October 2010 and September 2012. There were no requirements regarding continuous Medicaid coverage in the time prior to MLIP enrollment or in the year after MLIP release. However, previous analyses indicated that those with continuous coverage while enrolled in the MLIP had, on average, close to complete Medicaid coverage prior to enrollment as well (see Chapter 5).

For Aim 2 (Chapter 7), we used the same cohort specified above. Because we examined trajectories of dosages (average daily MMEs) of dispensed prescription opioids, beneficiaries in this cohort were followed from the first day of receiving any opioid prescription, as outlined above.

4.4 Study Population

Chapter 5 provides detailed descriptive information on demographics, comorbidities, and healthcare utilization of beneficiaries eligible for and enrolled in the NC MLIP. Specifically, beneficiaries enrolled in the MLIP were compared to those who were MLIP-eligible but not enrolled. Additionally, among enrolled beneficiaries, those completing the 12-month MLIP were compared to those who exited prior to 12 months.

Key findings included that MLIP-enrolled beneficiaries were more likely to have 1) substance use and mental health disorders, 2) obtained controlled substances from multiple pharmacies, and 3) visited emergency departments, as compared to beneficiaries who were eligible for, but not enrolled in the MLIP. Additionally, we found that compared to those who completed the 12-month MLIP, those who exited the MLIP early were 1) younger, 2) more

likely to obtain controlled substances from multiple pharmacies, 3) reside in counties with high opioid overdose death rates, and 4) have less stable Medicaid coverage prior to MLIP enrollment. Chapter 5 provides additional details on the study population. The descriptive analyses in Chapter 5 were helpful in understanding the composition of the cohort and informed the analysis conducted in Chapters 6 and 7.

4.5 Exposure Assessment

For Aim 1, the exposure of interest was having 12 months of exposure to the MLIP. We divided person-time into four segments: two pre-MLIP periods (>6 months pre-enrollment, or "pre-spike," and 0-6 months pre-enrollment, or "spike"), a 12-month program period ("lock-in"), and a period (up to 12 months) after program release ("post-release"). Descriptive analyses revealed a specific period with large spikes in numbers and dosages of CS dispensed, in the months just prior to program enrollment. This spike period precipitated MLIP enrollment for many beneficiaries. During this period, a sudden escalation was met by a similar de-escalation just prior to MLIP enrollment, resulting in dispensing that appeared to largely return to pre-spike levels just prior to actual enrollment. Moreover, additional analyses revealed that this pattern of escalation, triggering of MLIP criteria, and a nearly equal de-escalation was not unique to the MLIP-enrolled population (see Appendix A). It also occurred in Medicaid beneficiaries who were never enrolled in the MLIP but met the MLIP eligibility criteria. While this spike period revealed critical information regarding the average CS utilization trajectory leading to eligibility for the MLIP, this volatile period of utilization was likely not the most appropriate reference period for MLIP effect estimation. Rather, understanding the extent to which the MLIP was associated with CS utilization during and upon release, as compared to a more stable utilization

period prior to program enrollment provides a more suitable comparison. Therefore, we stratified pre-MLIP enrollment time into pre-spike and spike periods and focused our MLIP effect estimation on dispensing during lock-in and post-release periods as compared to the pre-spike period.

Enrollment in the MLIP and delineation of these four time periods were determined using the comprehensive, linked data set from the parent study. The DRIVE data set contained information on when beneficiaries were enrolled in Medicaid, as well as when they were enrolled in the MLIP.[105]

Aim 2 was also accomplished with the data assembled into pre-MLIP (i.e., pre-spike and spike periods), during lock-in, and post-MLIP release periods. For Aim 2, we used data on beneficiaries in the year prior to MLIP enrollment to assess covariates. These data allowed us to examine attributes of beneficiaries associated with heterogeneous patterns of longitudinal change. Because these covariates were assessed at the same time as trajectory pattern estimation, they are not considered predictors, but rather reveal key covariate associations.

4.6 Outcome Assessment

The outcomes of interest for Aims 1 and 2 included monthly numbers of dispensed CS prescriptions by payer source— Medicaid-reimbursed, not Medicaid-reimbursed (e.g., out-of-pocket), and those paid for using any source, as well as average daily dosages of dispensed opioid prescriptions, measured in terms of average daily MMEs.

Numbers of dispensed CS prescriptions were identified in Medicaid claims using NDCs, as well as a comprehensive list of 3-digit therapeutic class codes and 5-digit generic codes

provided by MLIP personnel. This list included all opioid medications, defined as having a therapeutic class code of H3A, H3H, H3J, H3M, H3N, H3U, or H3X. These include medications containing codeine, oxycodone, oxymorphone, hydrocodone, hydromorphone, fentanyl, morphine, and methadone, among others. Tramadol, also an opioid medication, was excluded from the list by excluding generic codes: 07221, 26387, 50417, 50427, 13909, as tramadol was not classified as a CS until mid-2014 and therefore would not have been included in the MLIP eligibility criteria for the study period. Benzodiazepine medications included in the list were those with therapeutic class codes of H2F (anti-anxiety class). However, Buspar/buspirone was excluded from the list by excluding 5-digit generic codes: 28891, 28892, 92121, 28890, 13037, and 19224, as it is not classified as a CS, and clonazepam/Klonopin was added to the list by including therapeutic class code H4B (anticonvulsant class) with generic codes 19467, 19468, 19469, 19470, 19472, 17470, 17471, or 17472, as it is a CS benzodiazepine. Additionally, NC MLIP restrictions specifically include "certain anxiolytics." While all benzodiazepine anxiolytics were included in the MLIP CS restrictions, the "certain anxiolytic" language was specifically added to the MLIP requirements to ensure meprobamate/Miltown was also captured under MLIP restrictions, as this medication is an anxiolytic but not a benzodiazepine.[108] Because this medication is also included in the H2F therapeutic class, it was easily captured in our analysis through the inclusion of that code.

To identify these same medications in the CSRS database, a crosswalk obtained through the UNC Lineberger's Comprehensive Cancer Center's Cancer Information & Population Health Resource that links therapeutic class codes, generic codes, and NDCs was used. Using the linked Medicaid-CSRS dataset, we obtained the number of opioid, benzodiazepine, and specific anxiolytic prescriptions dispensed per month to each beneficiary, stratified according to

reimbursement by Medicaid or not (i.e., those prescriptions captured in the CSRS without a corresponding Medicaid claim).

To examine dosages of opioids dispensed, we calculated the average daily MMEs dispensed per beneficiary. Because morphine has long been used as the standard of treatment for moderate to severe pain, it is often used as a reference or comparison point for other opioid medications.[109] MME conversion factors serve as a useful research tool to help compare opioid medication regimens, and research has suggested that a dose-dependent relationship exists between average daily MMEs and opioid overdose risk.[110-113] To calculate average daily MMEs, we used the following formula[109,114]

$$\text{Average Daily MMEs} = \frac{\text{(Drug strength)} * \text{(Drug quantity)} * \text{(MME conversion factor)}}{\text{Days' supply}}$$

Drug quantity and days' supply were obtained from the Medicaid claims-CSRS database, while drug strength and the MME conversion factors were available from CDC reference tables for each NDC. Table 4 displays the MME conversion factors used.[114-116]

Table 4. Opioid MME conversion factors

Opioid	MME conversion factor
Buprenorphine	
patch	12.6
tab or film	10
Butorphanol	7
Codeine	0.15
Dihydrocodeine	0.25
Fentanyl	
buccal or sublingual tablets, or	
lozenges/troche	0.13
film or oral spray	0.18
nasal spray	0.16
patch	7.2
Hydrocodone	1
Hydromorphone	4
Levorphanol tartrate	11
Meperidine hydrochloride	0.1
Methadone	3
Morphine	1
Nalbuphine	1
Opium	1
Oxycodone	1.5
Oxymorphone	3
Pentazocine	0.37
Tapentadol	0.4

For Aim 1, the average daily MME for each prescription was applied to all days for which the prescription was active (i.e., all days in which the prescription was to be taken, according to the days' supply). If a beneficiary had more than one opioid prescription active on a given day, the MMEs for that day were summed. For Aim 2, we averaged each beneficiary's average daily MMEs across each calendar month. We then log transformed this monthly average to obtain an approximately normal distribution for improved model estimation, consistent with previous research.[88]

Similar dosing equivalencies for benzodiazepines are less evidence-based, poorly described, and often based on expert opinion. Moreover, the majority of CS prescriptions received by MLIP-enrolled beneficiaries consisted of opioids (approximately 75-80%); therefore, we did not calculate similar dosage estimates for benzodiazepines.

4.7 Covariate Assessment

To elucidate potential confounding variables that could have impacted our estimation of the effect of exposure to the NC MLIP on dispensed CS prescriptions and dosages of opioids dispensed (i.e., Aim 1), we developed a conceptual figure (Figure 4). This figure was based on the best available literature and our understanding of factors affecting MLIP exposure and post-MLIP CS utilization.

Additionally, for Aim 2, we examined heterogeneity in trajectories of beneficiaries' dispensed opioid dosages across periods prior to, during, and following release from the MLIP, as well as the attributes of beneficiaries that are best captured by the different trajectories. By exploring characteristics of beneficiaries in the year prior to MLIP enrollment, we were able to develop insight into the trajectories that different groups of beneficiaries might follow when enrolled and upon disenrollment, as well as the attributes of those who could potentially benefit from additional or different types of public health interventions (e.g., increased case management support; complementary or alternative treatment approaches, such as physical therapy; screening for medication-assisted therapy). As previously mentioned, we hypothesized that trajectories would differ according to the following covariates: age, comorbidity burden, and recent history of mental health disorders, pain conditions, and substance use disorders.

Figure 4. Conceptual model of general relationships between exposure, outcomes, and covariates

Demographic
Age
Sex
Race/ethnicity
Medicaid eligibility category
Medicaid class code

Environmental
Urbanicity in county of residence
Overdose death rate in county of residence
Overdose prevention policies and activities

MLIP exposure

CS dispensed
prescriptions dispensed
Dosage dispensed (MMEs)

Health-related
Substance abuse or dependence disorders (including use of MAT)
Overdose events
Chronic pain conditions
Mental health disorders (e.g., depression, anxiety)
General comorbidity
Healthcare use and access (e.g., pharmacies visited, ED visits, inpatient admissions)

Chapter 5 and Appendix B provide specific information on covariate categories and claims-related codes used to define covariates, as well as information on the prevalence of these characteristics in the MLIP population. Below, we briefly provide general information about each of these covariates, as well as what is known regarding associations between each of these covariates and CS use and overdose.

- Age: Research indicates that young and middle-aged adults are most likely to nonmedically use prescription drugs and experience overdose events.[42,117,118] According to the CDC, drug overdose death rates are highest among those ages 45-49 years.[119]

- Sex: The literature indicates a complex relationship between sex and prescription drug misuse, abuse, and overdose.[42] While men report nonmedical use of prescription drugs more often than women, some studies suggest that women are more likely to be prescribed opioids, to use them chronically, and to doctor-shop and pharmacy-shop (i.e., obtain prescriptions from many different doctors or pharmacies), as compared to men.[117,120-122] Additionally, while men are more likely to experience a fatal drug overdose, women and men experience similar rates of ED visits due to nonmedical use of prescriptions.[1,123]

- Race/ethnicity: American Indians, Alaska Natives, and non-Hispanic Whites are more likely to report nonmedical use of prescription drugs and have the highest fatal overdose rates.[1,42] Additionally, research suggests that African Americans and Hispanics are less likely to be prescribed any drug, including CS.[42,124,125]

- Medicaid eligibility category: Provides information on criteria met to qualify for Medicaid benefits. Medicaid benefits were available to the following major groups of NC residents: 1) those who were pregnant and had household incomes up to about 200% of the federal poverty level; 2) parents with dependent children and household incomes up to about 45% of the federal poverty level (e.g., for a family of three, income cannot exceed $667/month); 3) blind persons with incomes below the poverty limit; 4) persons under the age of 65 years who were unable to work due to a severe disability that was expected to last at least 12 months and had incomes below the poverty limit; 5) persons aged 65 years or older with incomes below the poverty limit; 6) certain adults with long-term care needs (e.g., nursing care for older adults, others with long-term disabilities); and 7) children whose caregivers' incomes fell below 133% or 210% of the poverty limit,

49

depending on the child's age.[7] Those in the latter three groups were not included in our analyses (see Section 4.3).

- Medicaid class code: Provides further information on Medicaid qualification. Most Medicaid beneficiaries qualify for Medicaid under a "categorically needy" class code, indicating that certain income requirements were met as determined by the specific aid category (e.g., families with dependent children, disabled). However, other routes through which individuals may qualify include a "medically needy" classification in which a person may have not satisfied financial eligibility requirements (i.e., their income was too high) but significant medical expenses reduced their income below a certain level that then qualified them as "medically needy."[126]

- Urbanicity in county of residence: Research suggests that prescription opioid misuse and abuse may disproportionately affect rural, as compared to urban areas.[127-129] In North Carolina specifically, higher rates of both prescription opioid sales and overdoses have been detected in the rural southern and western corners of the state.[130] The U.S. Department of Agriculture's 2013 rural-urban continuum codes were used to classify counties into one of nine categories.[131] This classification system assigns categories to metropolitan counties based on their population size and assigns categories to nonmetropolitan counties based on their degree of urbanization and how close they are to a metropolitan area.

- Overdose death rate in county of residence: County overdose death rates were obtained from the NC Division of Public Health (DPH).[132] Death rates were averaged over the period of 2008 through 2013 and counties were grouped into quintiles according to their average rate. Death rates were reported as per 100,000 population per year.

- Overdose prevention policies and activities: During the time period under study (i.e., 2009-2013), several overdose prevention and awareness-raising activities took place in the state of NC. These included the statewide implementation of Project Lazarus, a community-based, multi-component overdose prevention intervention; increased availability of medicine drop boxes and drug take-back events, passage of a 911 Good Samaritan law; and increased used of naloxone distribution programs; among other activities.[133] To help control for time trends that may be due to these prevention activities, as well as general changes in awareness and CS prescribing culture and use during this time, we generated temporal trend measures that allowed us to control for changes in outcomes occurring over calendar time. We generated these measures from temporal trends in outcome measures in the population of Medicaid beneficiaries who were eligible to enter the MLIP, but were never enrolled. These temporal trend measures were included in all Aim 1 models (see Chapter 6). For further details on temporal trend generation, see Appendix C.

- Substance use disorders: Several studies have suggested that substance abuse or dependence disorders are associated with prescription opioid use, misuse, and abuse.[45,134-138] These disorders include those related to illicit substances (e.g., heroin, cocaine), alcohol, tranquilizers, and sedatives. Chapter 5 and Appendix B provide information on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes used to capture substance use disorders in our data. These codes were identified from the Agency for Healthcare Research and Quality's (AHRQ) Clinical Classification Software (CCS). The CCS provides a diagnosis categorization scheme for ICD-9-CM codes to collapse coding into clinically meaningful categories.[139]

- Medication-assisted treatment: Defined as any prescription claim for a buprenorphine product indicated for use of opioid addiction treatment or any mention of Current Procedural Terminology (CPT) code H0020, "Alcohol and/or drug services; methadone administration and/or service (provision of the drug by a licensed program)."[140,141]

- Overdose events: We used an ICD-9-CM definition for medication and drug-related overdoses developed by the NC DPH, in collaboration with the UNC's Injury Prevention Research Center, through a CDC-funded surveillance quality improvement initiative to improve injury surveillance for outcomes, such as overdoses.[142-144] The definition was developed using existing state and national organization definitions; advice from content experts in injury epidemiology, surveillance methods, and public health informatics; and end user feedback.

- Pain conditions: Specific types of pain, namely back and headache pain, are specifically associated with heavy opioid use in Medicaid populations.[136,138] As the number of pain diagnoses increases, the likelihood of heavy opioid use has also been found to increase. Chapter 5 and Appendix B provide information on the ICD-9-CM codes that were used to capture specific pain diagnoses in our data. These categorizations have been used in previous research and have been shown to be the most commonly reported chronic pain sites and reasons for long-term opioid use in a general medical population.[135,136,145]

- Mental health disorders: Research suggests that the presence of mental health disorders are associated with increased use of opioids and nonmedical use of opioids.[10,45,134,146-151] These mental health conditions included mood (e.g., depression, bipolar) disorders, as well as conditions characterized by panic symptoms, social phonic/agoraphobic symptoms, and a history of severe psychological distress. Consistent with previous

research, AHRQ's CCS definitions were used in classifying beneficiaries' as having mood and/or anxiety disorders.[139,152] Mood disorders included depressive and bipolar conditions, and anxiety disorders included panic disorder, generalized anxiety disorder, social phobia, and obsessive-compulsive disorder, among others.[152] Chapter 5 and Appendix B provide further information on definitions used.

- General comorbidity: The Charlson comorbidity score was used as a measure of a given beneficiary's overall medical comorbidity.[153,154] Research has shown that patients prescribed greater doses of opioids also have higher Charlson comorbidity scores on average.[111,155] Moreover, using this same CSRS-Medicaid linked data set, Roberts (2015) found that having a high Charlson comorbidity score was associated with having a circumvented prescription fill.[79]

- Healthcare utilization and access: To assess overall healthcare utilization and access to healthcare,[156-158] we examined beneficiaries' number of pharmacies visited, number of ED visits, and number of inpatient admissions in the year prior to MLIP enrollment. Appendix B provides additional information on codes that were used to capture counts of unique pharmacies used, ED visits, and inpatient admissions.

4.8 Statistical Analysis

To accomplish Aims 1 and 2, we used models that took advantage of the rich, longitudinal nature of our data. Specifically, for Aim 1, we used GEE to estimate measures of association between MLIP-related time periods and the average number of CS prescriptions dispensed per person-month and the dosage (average daily MMEs) of dispensed opioids per person. To examine changes in numbers of CS dispensed per person-month, we used both linear-

Poisson and log-Poisson GEE models to estimate count differences and count ratios, respectively. A linear regression GEE (identity link, Gaussian residual distribution) was used to estimate changes in average daily MMEs per person while locked-in and in the year following release, as compared to a pre-MLIP period (i.e., the pre-spike period).

For Aim 2, LCGA models, also known as group-based trajectory models, were used to examine heterogeneity in trajectories of dosages (MMEs) of opioids dispensed across periods prior to, during, and following release from the MLIP.[85-90,94] Conventional modeling often assumes that a sample is drawn from a single population, characterized by a single set of parameters (e.g., means, variances, covariances).[159] Finite mixture modeling, which LCGA is an application of, relaxes these assumptions and allows for the estimation of different sets of parameters across dissimilar subgroups for which there are no deterministic classifiers observed.[96,160] While certain finite mixture modeling applications, such as growth mixture modeling, assume that the population is composed of distinct subgroups (e.g., true substance abusers, non-abusers, diverters), which can be defined by their trajectories over time, LGCA takes a less literal interpretation.[160,161] LCGA is still used to disentangle and describe underlying heterogeneity by identifying qualitatively and quantitatively different patterns of change within a larger population; however, it does not assume that different trajectories represent specific subgroups. Rather, it can be thought of as a "statistical approximation tool" that uses trajectory groups to estimate an unknown distribution of trajectories across the larger population.[95-98,161] These trajectory groups, or "points of support," help summarize and depict regions across the underlying distribution. Nagin, who first proposed the LCGA approach, was careful to emphasize the interpretation of results from these models: "…that the groups should not be interpreted as literal entities. Instead, they should be thought of as latent longitudinal strata in the

data that are composed of individuals following approximately the same development course on the outcome of interest. These strata identify distinctive longitudinal features of the data." [96,97,161]

As with the analysis approach used for Aim 1, LCGA models are well-suited to our study design, as they can accommodate data available at irregular intervals and missing data, assuming data are missing at random.[92] Additionally, LCGA has been previously used to study substance use trajectories and types of users, as discussed in Chapter 3. While LCGA has not been used to study how beneficiaries' trajectories of dosages of dispensed opioids might differ and change across MLIP pre-enrollment, enrollment, and disenrollment periods for different strata of the beneficiary population, previous research on characteristics related to CS use trajectories across time for other populations, as well as previous NC MLIP research, provided a general basis for hypothesizing what we might find, as outlined in Chapter 3.[79,84-91]

A key difference in the analytic approaches for Aims 1 and 2 is that in Aim 1, we were ultimately interested in estimating average population measures of effect to understand policy impacts of exposure to the MLIP on average CS-related measures. However, for Aim 2, we explored whether summary population measures of effect do not tell the whole story for this beneficiary population, and we allowed for different underlying trajectories across the population.

In Chapters 5-7, we provide additional details on analytic methods used to fulfill Aims 1 and 2. All analyses were carried out in SAS version 9.4 (Cary, NC) and Mplus version 7.4. This dissertation was approved by the University of North Carolina at Chapel Hill's Institutional Review Board.

CHAPTER 5 – CHARACTERISTICS OF NORTH CAROLINA MEDICAID BENEFICIARIES ELIGIBLE, ENROLLED, AND RETAINED IN A "LOCK-IN" PROGRAM (MANUSCRIPT 1)

5.1 Overview

Objective: Describe characteristics of North Carolina (NC) beneficiaries in a Medicaid "lock-in" program (MLIP)

Data Source: NC Medicaid claims, June 2009-June 2013

Study Design: Prospective cohort

Methods: Demographics, co-morbidities, and healthcare utilization were extracted from Medicaid claims. Beneficiaries enrolled in the MLIP were compared to those who were MLIP-eligible but not enrolled. Among enrolled beneficiaries, those completing the 12-month MLIP were compared to those who exited prior to 12 months.

Principal Findings: Compared to beneficiaries who were eligible for, but not enrolled in the MLIP, enrolled beneficiaries were more likely to have 1) recorded diagnoses of substance use and mental health disorders, 2) obtained controlled substances from multiple pharmacies, and 3) visited emergency departments. Compared to those who completed the 12-month MLIP, those who exited the MLIP early were 1) younger, 2) more likely to obtain controlled substances from multiple pharmacies, 3) reside in counties with high opioid overdose death rates, and 4) have less stable Medicaid coverage prior to MLIP enrollment.

Conclusions: NC's MLIP appears to be successful in identifying subpopulations that may benefit from provision and coordination of services, such as substance abuse and mental health services. However, there are challenges in retaining this population for the entire MLIP duration.

5.2 Introduction

The public health epidemic of prescription drug misuse carries enormous health, social, and economic impacts. Between 2000 and 2015, the annual prescription drug overdose death rate in the U.S. more than tripled from 2.8 to 9.2 deaths per 100,000 population.[1] Of the 29,728 lives lost to prescription drug overdoses in 2015, three out of four deaths involved an opioid analgesic and nearly one-third involved a benzodiazepine.[1] Because both types of drugs act as central nervous system depressants, combined use considerably increases a person's risk of overdose.[110]

Medicaid beneficiaries are a particularly high-risk population for prescription drug overdose. Medicaid beneficiaries are prescribed opioids at twice the rate of persons without Medicaid benefits, and their prescription opioid overdose death rates are three to eight times that of those without Medicaid benefits.[9,10,15-17] State-based Medicaid "lock-in" programs (MLIPs) are a widely used strategy for addressing the potential misuse and abuse of prescription drugs in Medicaid populations.[33,34] MLIPs are designed to identify Medicaid beneficiaries demonstrating potential overutilization of prescription drugs and to limit their access, generally through requiring beneficiaries to use a single prescriber and/or pharmacy to obtain certain types of prescribed drugs (e.g., opioids, benzodiazepines) for a specified period of time.[34]

"Lock-in" programs are increasingly being implemented or proposed in non-Medicaid populations, such as those who are privately insured and those who receive Medicare,[162-164] despite limited evaluation of these programs and knowledge of the populations impacted.[20,165] Initial "lock-in" program studies largely focused on cost savings to Medicaid, as well as documenting some reductions in medical and pharmacy utilization measures.[34,35,48,72] More recent research indicates that MLIPs may have unintended consequences in the form of increased out-of-pocket prescription fills for opioids and benzodiazepines, which potentially could attenuate the utility of these programs as an overdose prevention measure.[83]

In order to understand and improve the utility of MLIPs, we need more information about the attributes of beneficiaries selected into these programs, including their health care needs. The purpose of this study was to examine and compare demographic and clinical characteristics of beneficiaries enrolled in North Carolina's (NC) MLIP, as compared to individuals found eligible for enrollment but not enrolled into the program. Additionally, we sought to compare those who were retained in the MLIP for the entire 12-month program period relative to those who exited the MLIP prior to program completion.

5.3 Methods

NC Medicaid claims data from June 2009 through June 2013 were obtained from the NC Division of Medical Assistance (DMA).

North Carolina MLIP Enrollment

58

NC's MLIP originated in October 2010.[40] Eligibility criteria for the program included

meeting any of the following criteria within a two consecutive calendar month period: (1) filling

more than six opioid prescriptions, (2) filling more than six benzodiazepine prescriptions, or (3)

filling opioid or benzodiazepine prescriptions that were written by more than three different

prescribers.[40] Each month a vendor, contracting with the DMA, reviewed prescription dispensing

data for all NC Medicaid beneficiaries in the previous two calendar months to determine who

met MLIP eligibility criteria. The vendor then ranked the MLIP-eligible pool of beneficiaries

using a proprietary algorithm that factored in the number, quantity, and days' supply of

prescriptions obtained, paid amounts, and distinct prescribers and pharmacies visited, combined

with a clinical review process by pharmacists employed by the vendor. Each month,

approximately 200 of the highest ranking beneficiaries were then recommended to DMA for

MLIP enrollment. Therefore, not everyone who was eligible was selected for MLIP enrollment.

The specific algorithm and review process details were proprietary and thus unavailable;

however, as outlined below, our analysis was structured to gain insight into the attributes

considered in these processes, as well as characteristics that may not have been included in these

processes but could indicate important health needs of the beneficiaries examined. Upon

approval from the DMA, the approximately 200 selected beneficiaries each month were each

sent a letter notifying them of their upcoming enrollment in the program and that the MLIP

restricted them to using one prescriber and one pharmacy location to obtain prescriptions

categorized as opioids or benzodiazepines for a one-year period. Beneficiaries were given 30

days to choose a preferred prescriber and pharmacy before restrictions began. Those who did not

respond to the DMA were assigned to a prescriber and pharmacy. These administrative processes

took approximately two months to complete. That is, beneficiaries who were selected for

enrollment based on meeting eligibility criteria in the two-month period of June and July were generally enrolled in the MLIP in October.

Study cohorts

The overall study population consisted of adults ages 18-64 years enrolled in Medicaid at any point between June 2010 and December 2012. We first identified the MLIP-eligible population by examining Medicaid-reimbursed prescription fills from June 2010 through December 2012 to determine who would have been eligible for MLIP enrollment when the program began in October 2010 through the end of our dataset in June 2013. For each two calendar month period, we examined the number of opioid and benzodiazepine prescriptions obtained by each beneficiary. Consistent with MLIP eligibility criteria, beneficiaries with more than six opioid or benzodiazepine prescriptions in a consecutive two-month period were defined as MLIP-eligible (Figure 5.1). While beneficiaries could also become eligible by obtaining these prescriptions from more than three unique prescribers (see third criterion above), the data available did not provide accurate information on numbers of unique prescribers. Therefore, we were unable to use the third criterion in constructing our MLIP-eligible population.

Within the MLIP-eligible population, we then identified a second study cohort that was actually enrolled in the MLIP (Figure 5.1). As specified in this figure, this cohort was then further stratified based on time spent in the MLIP, categorized as (Group 1) those spending no time in the MLIP, because they no longer possessed Medicaid coverage during the time they would have been enrolled; (Group 2) those who were enrolled in the MLIP for part of their assigned period but discontinued Medicaid coverage at some point during their entire observed and assigned MLIP period; (Group 3) those who possessed Medicaid coverage during the

proportion of their MLIP period observed in our data (i.e., through June 2013), but their entire

one year MLIP period exceeded the time observed in our dataset (i.e., they were administratively

censored); and (Group 4) those who were observed for their full 12-month MLIP enrollment

period and possessed Medicaid coverage during the entire time. Due to similarities, the first two

groups and last two groups were collapsed in several analyses in which the combined first two

groups were termed the "early exiters" and the combined last two groups, the "completers."

Finally, to place our findings within the context of the larger Medicaid population, we

compared these distinct cohorts to a sample of the general Medicaid population restricted to the

same age range and within the same time period (i.e., any Medicaid beneficiary ages 18-64 years

with at least one pharmacy claim between October 2009 and September 2010).

Measures

For MLIP-eligible beneficiaries, all demographic and clinical characteristics were

assessed at the time they became MLIP-eligible. For the general Medicaid sample, all

demographic characteristics were assessed at the time of the first pharmacy claim between

October 2009 and September 2010.

Demographic measures

Demographic characteristics included age, sex, race, urbanicity of county of residence,

drug overdose death rate in county of residence, Medicaid aid category, and Medicaid class code.

The U.S. Department of Agriculture's 2013 rural-urban continuum codes were used to classify

counties according to urbanicity.[131] County overdose death rates were obtained from the NC

Division of Public Health.[4] Death rates were averaged over the period of 2008 through 2013 and

counties were grouped into quintiles according to their average rate. Medicaid aid categories and

class codes provide information on criteria met to qualify for Medicaid benefits. The most

common NC Medicaid aid categories include (1) parents with dependent children and a

household income < 45% of the federal poverty level, (2) persons under the age of 65 years who

are unable to work due to a severe disability that is expected to last at least 12 months, and (3)

pregnant women with household incomes < 196% of the federal poverty level. Class codes

provide further information on Medicaid qualification. Most Medicaid beneficiaries qualify for

Medicaid under a "categorically needy" class code, indicating that certain income requirements

were met as determined by the specific aid category (e.g., families with dependent children,

disabled). However, other routes through which individuals may qualify include a "medically

needy" classification in which a person may have not satisfied financial eligibility requirements

(i.e., their income was too high) but significant medical expenses reduced their income below a

certain level that then qualified them as "medically needy."[126]

Substance use-related utilization, overall healthcare utilization, and comorbid condition

measures

For the MLIP-eligible population, we also examined beneficiary-level clinical

characteristics, including controlled substance-related characteristics, overall health care

utilization, and other comorbid conditions in the 12 months prior to MLIP eligibility. Controlled

substance-related characteristics included MLIP eligibility criteria met, number of unique

pharmacies visited in the two-month period prior to MLIP eligibility, and history of medication-

assisted treatment or overdose in the previous year. Beneficiaries were classified as having

received medication-assisted treatment in the prior year if they had filled a prescription for a

buprenorphine product indicated for use of opioid addiction treatment or if there was any

mention in their claims of Current Procedural Terminology (CPT) code H0020 for methadone

treatment, consistent with previous research.[114,166] The International Classification of Diseases,

Ninth Revision, Clinical Modification (ICD-9-CM) definitions used to determine which

beneficiaries had experienced an overdose were developed by the NC Division of Public Health,

in collaboration with the UNC's Injury Prevention Research Center, through a CDC-funded

surveillance quality improvement initiative to improve injury surveillance for outcomes, such as

overdoses.[167] Slight modifications were made to also specifically include benzodiazepine-related

overdoses (a target of the MLIP).

Healthcare utilization measures included numbers of emergency department (ED) visits

and inpatient admissions and the number of days with Medicaid coverage in the prior year.

Finally, we estimated the prevalence of various pain-related, mental health, substance use-

related, and other comorbid diagnoses. Detailed reference information regarding the ICD-9-CM

definitions used to define each specific condition can be found in the footnotes below Table 5.3.

Statistical Methods

We estimated and compared the prevalence of demographic and clinical characteristics of

NC Medicaid beneficiaries enrolled in the MLIP to those who were eligible, but not ultimately

enrolled. We also compared these groups to the general Medicaid population with respect to key

demographic characteristics. Lastly, we compared the prevalence of demographic and clinical

characteristics of beneficiaries enrolled in the MLIP, stratified by time spent in the MLIP. For

categorical variables, we obtained counts and percentages. For continuous variables, we

calculated means and standard deviations. For heavily skewed continuous variables (i.e., health care utilization measures), we report means and 25th, 50th (median), and 75th percentiles.

For all variables, we calculated standardized differences between those enrolled in the MLIP and those eligible but not enrolled, as well as between MLIP "early exiters" and "completers."[168] Standardized differences provide a measure of the similarity or dissimilarity of two groups with respect to specific covariates. For continuous and binary covariates, standardized differences were used to compare the means of two groups in units of the pooled standard deviation of the two groups. For categorical variables with more than two levels, an overall standardized difference was calculated, using a multivariate Mahalanobis distance method.[168] All analyses were completed in SAS 9.4. This study was approved by the University of North Carolina at Chapel Hill's Institutional Review Board.

5.4 Results

Demographics of MLIP-eligible, MLIP-enrolled, and MLIP-completers

Between June 2010 and December 2012, a total of 17,407 NC Medicaid beneficiaries ages 18-64 years received more than 6 opioid prescriptions and/or more than 6 benzodiazepine prescriptions through Medicaid in a two consecutive calendar month period, qualifying them for the MLIP (Table 5.1). Compared to the general NC Medicaid population, those who met MLIP eligibility criteria tended to be older, more often male, more often white, more often from counties with high overdose death rates, and less likely to receive Medicaid benefits due to a pregnancy.

Among those eligible for the MLIP, 31% were enrolled in the MLIP (Table 5.1). Compared to those not enrolled, MLIP-enrolled beneficiaries were more often younger (mean age 37.1 vs. 41.0), more often female (69.1% vs. 63.2%), less often qualified for Medicaid benefits due to disability (36.1% vs. 48.3%), and more often as a family with dependent children (60.8% vs. 48.5%) (Table 5.1, Figure 5.2A).

Among those enrolled, 41% remained in the program for a full 12 months, and another 25% remained in the MLIP until the point of administrative censoring. Together, we refer to these beneficiaries as "completers." Another 25% spent less than 12 months in the MLIP despite our ability to follow them and observe them for a longer period of time, and 8% spent no time in the MLIP. Together, we refer to these beneficiaries as "early exiters." The two groups constituting MLIP "completers" were generally similar in terms of major demographic and clinical characteristics, as were the two groups constituting "early exiters."

Compared to MLIP "completers," the "early exiters" tended to be younger (34.1-34.4 vs. 38.6-38.5), white (82.9-84.9% vs. 72.5-73.7%), more often from counties with high overdose death rates (46.4-46.8% vs. 38.1-39.8% in the top 2 overdose death rate quintiles), more often received aid as a family with dependent children or due to a pregnancy, and more often qualified as medically needy (11.1-15.8% vs. 3.0-3.8%) (Table 5.1, Figure 5.2B).

Substance-related and health care utilization of MLIP-eligible, MLIP-enrolled, and MLIP-completers

Nearly all of those who became eligible for the MLIP met the opioid eligibility criterion; however, those enrolled in the MLIP also visited more unique pharmacies to fill their opioid

65

and/or benzodiazepine prescriptions than did those not enrolled (Table 5.2; Figure 5.2). Twenty-nine percent of those enrolled obtained these drugs from more than three different pharmacies in a two-month period, as opposed to 7.8% of those not enrolled. Moreover, "early exiters" had an even higher prevalence than "completers" of using many different pharmacies (i.e., 35.8-40.4% vs. 23.7-26.3%).

With the exception of ED use, other healthcare utilization measures were generally similar between those who were and were not enrolled in the MLIP. Those enrolled had, on average, twice as many ED visits (mean=8.3 vs. 4.2) in the year prior to becoming eligible (Table 5.3; Figure 5.2). MLIP-enrolled and non-enrolled cohorts tended to have similar Medicaid coverage in the prior year. However, stratification by time spent in the MLIP revealed that "early exiters" tended to have less stable Medicaid coverage in the prior year (i.e., fewer days enrolled in Medicaid in the prior year).

Comorbid conditions of MLIP-eligible, MLIP-enrolled, and MLIP-completers

Beneficiaries enrolled in the MLIP tended to a have a higher prevalence of pain, mental health, and substance use-related conditions (Table 5.3; Figure 5.2). Of note, nearly a quarter of those enrolled had a substance use disorder diagnosis in the year prior (23.3%), almost double that of those not enrolled (13.5%). The prevalence of other comorbid conditions was generally similar between MLIP-enrolled and non-enrolled cohorts except that the latter had a higher proportion of recent cancer diagnoses (13.3% vs. 0.8%). Stratification by time spent in the MLIP revealed an even higher prevalence of pain, mental health, and substance use-related conditions among those who completed the MLIP.

5.5 Discussion

This study identified many differences between the NC MLIP target population (as defined by program selection criteria) and the actual population enrolled in and impacted by the program. Selection for the MLIP included a prioritization process of all eligible beneficiaries since, due to resource constraints, only a limited number of those eligible could be enrolled in any given month. Those enrolled in the MLIP tended to be younger, female, and less often qualified for Medicaid benefits due to a disability and more often as a family with dependent children. Additionally, those enrolled tended to visit more pharmacies to fill their opioid and/or benzodiazepine prescriptions, have more ED visits, have a higher prevalence of pain-, mental health-, and substance use-related conditions, and have a lower prevalence of recent cancer diagnoses relative to those eligible but not enrolled in the MLIP. Beneficiaries with cancer diagnoses were generally excluded from MLIP enrollment.

To further understand the extent to which beneficiaries were exposed to the program, we stratified the population of those enrolled by time spent in the MLIP. Those who exited the program early were more often younger, white, and from counties with high overdose death rates, compared to those who remained in the program. Additionally, we found that "early exiters" more often received aid as a family with dependent children or due to a pregnancy, qualified as medically needy, visited more unique pharmacies to fill their opioid and/or benzodiazepine prescriptions, had less stable Medicaid coverage in the prior year, and a lower prevalence of diagnoses for pain-, mental health-, and substance use-related conditions. These population profiles not only illuminate important generalizability considerations but also care coordination opportunities for future MLIP design.

The generalizability of MLIP evaluation findings is an important consideration as the medical community continues to grapple with the surging opioid epidemic and "lock-in" programs are implemented more broadly. "Lock-in" programs have been increasingly utilized in new and different beneficiary populations, including private insurance plans, other Medicaid populations, and will soon be incorporated into Medicare.[162-164] While the evidence base for these programs is sparse, recent evaluation findings from NC's MLIP have begun to provide a more holistic understanding of both intended and unintended consequences of the MLIP. Skinner et al. (2016) reported that when compared to pre-enrollment, enrollment in the NC MLIP was associated with obtaining fewer Medicaid-reimbursed opioid prescriptions, visiting fewer unique pharmacies to obtain these medications, and reductions in Medicaid expenditures.[80] However, Roberts et al. (2016) provided a different perspective, finding that compared to pre-enrollment, enrollment in the NC MLIP was associated with a four-fold increase in the rate of paying cash for one's opioids or benzodiazepines despite having Medicaid coverage, revealing a key weakness of the program.[83] These are the first known findings to highlight and contrast the intended and unintended consequences of an MLIP and should alert current and future "lock-in" program administrators to consider the full range of the program's potential impacts. As the evidence base develops and as these programs are designed and refined, evaluations from other "lock-in" programs are needed that not only present a range of program impacts, but also provide a clear depiction of the affected population. Our findings indicate a largely young, white, female population is selected for MLIP enrollment that has a high prevalence of mental health comorbidities, high ED use, and often utilizes many different pharmacies to obtain controlled substances. Moreover, about one-third of this population was characterized by unstable Medicaid coverage, including incomplete enrollment in the MLIP and incomplete Medicaid coverage in

the year prior. The extent to which observed impacts (e.g., reductions in Medicaid-reimbursed opioid prescriptions but increases in out-of-pocket opioid prescriptions) in this beneficiary population transfer to "lock-in" programs in private insurance, older adult, and other populations is not known and will be an important consideration for future research.

Even with our limited view of complete "lock-in" program impacts, these programs theoretically provide a unique opportunity to efficiently deliver services capable of improving beneficiary health and saving healthcare dollars. We found that beneficiaries enrolled in the MLIP tended to have a high prevalence of comorbidities, including pain-, mental health-, and substance use-related conditions, and tended to show signs of uncoordinated care (e.g., high use of EDs and multiple pharmacies). The ability of "lock-in" programs to more effectively target the complex health needs of this beneficiary population is unknown, but has strong potential. In 2014, the Association for Community Affiliated Plans supported implementation of innovative MLIP pilot projects in Medicaid populations in four different states.[68] These pilot projects offered a more holistic MLIP model, as compared to the more traditional MLIP model (like the one administered in NC). Program elements included connections to pain specialists, risk screenings, evaluation of barriers to critical needs (e.g., transportation, housing) and connection to resources, and screening and referral to substance abuse treatment resources. Moreover, case managers were assigned to MLIP beneficiaries in at least two of these projects to help further coordinate care. While evaluation research was limited to short-term outcomes, preliminary results revealed cost savings and improved care coordination. Pending further evaluation, such models, particularly when targeted to the needs of specific "lock-in" program beneficiary populations, may serve as a more effective framework. Based on our findings, inclusion and coordination of substance abuse and mental health screenings and connection to substance abuse,

mental health, and alternative pain therapy services could serve as a useful starting point for improving and piloting a more comprehensive MLIP model in NC.

Our findings should be viewed in light of four limitations. First, as noted above, the Medicaid data available did not include accurate information on numbers of unique prescribers, as the claims data provided did not possess a reliable prescriber identifier. Therefore, we were unable to use the third criterion in constructing our MLIP-eligible population. However, given that almost all of the MLIP-enrolled cohort met the first criterion (i.e., more than six opioid prescriptions) and given that there were likely relatively few people who visited several unique prescribers but did not also meet the prescription thresholds, we would not expect this missing information to have excluded many beneficiaries from our analysis. Second, our measurement of overdoses in the prior year only captured overdoses involving some interaction with the health care system while a person had Medicaid coverage. Third, the extent to which pain-related diagnoses represented actual pain-related conditions is unknown. It is possible that some beneficiaries were drug-seeking and did not have a painful condition; therefore, the prevalence of these conditions may be overestimated. However, poor coding of the conditions on claims could also lead to underestimation. Fourth, the presence of diagnoses in the year prior to meeting MLIP eligibility may be underestimated, particularly for "early exiters," as they also tended to have less Medicaid coverage in the prior year. Findings stratified by time spent in the MLIP should be viewed with this limitation in mind. However, research suggests that inclusion of any available data in a lookback period to assess presence of covariates results in less misclassification than restricting the data to a common lookback period for all persons (i.e., a restricted period in which everyone has Medicaid coverage for the entire time).[169]

Attributes of the population impacted by the MLIP provide key insights into the generalizability of observed MLIP impacts to other target populations and opportunities for improved care models among "lock-in" program populations. Future work should aim to examine a broad range of potential positive and negative impacts of these programs, combined with a clear description of studied populations, so that future program designs can be informed by the most comprehensive and relevant research. While "lock-in" program administrators should aim to gain a thorough understanding of the specific beneficiary populations impacted by their programs, our findings can help prepare administrators of new, similar "lock-in" programs for the magnitude of substance use and comorbidity that may be likely in their populations.

Figure 5.1 Classification of persons who qualified for the North Carolina Medicaid Lock-in Program (MLIP) from June 2010 through December 2012, stratified by enrollment in the MLIP and time spent in the MLIP (among those enrolled)
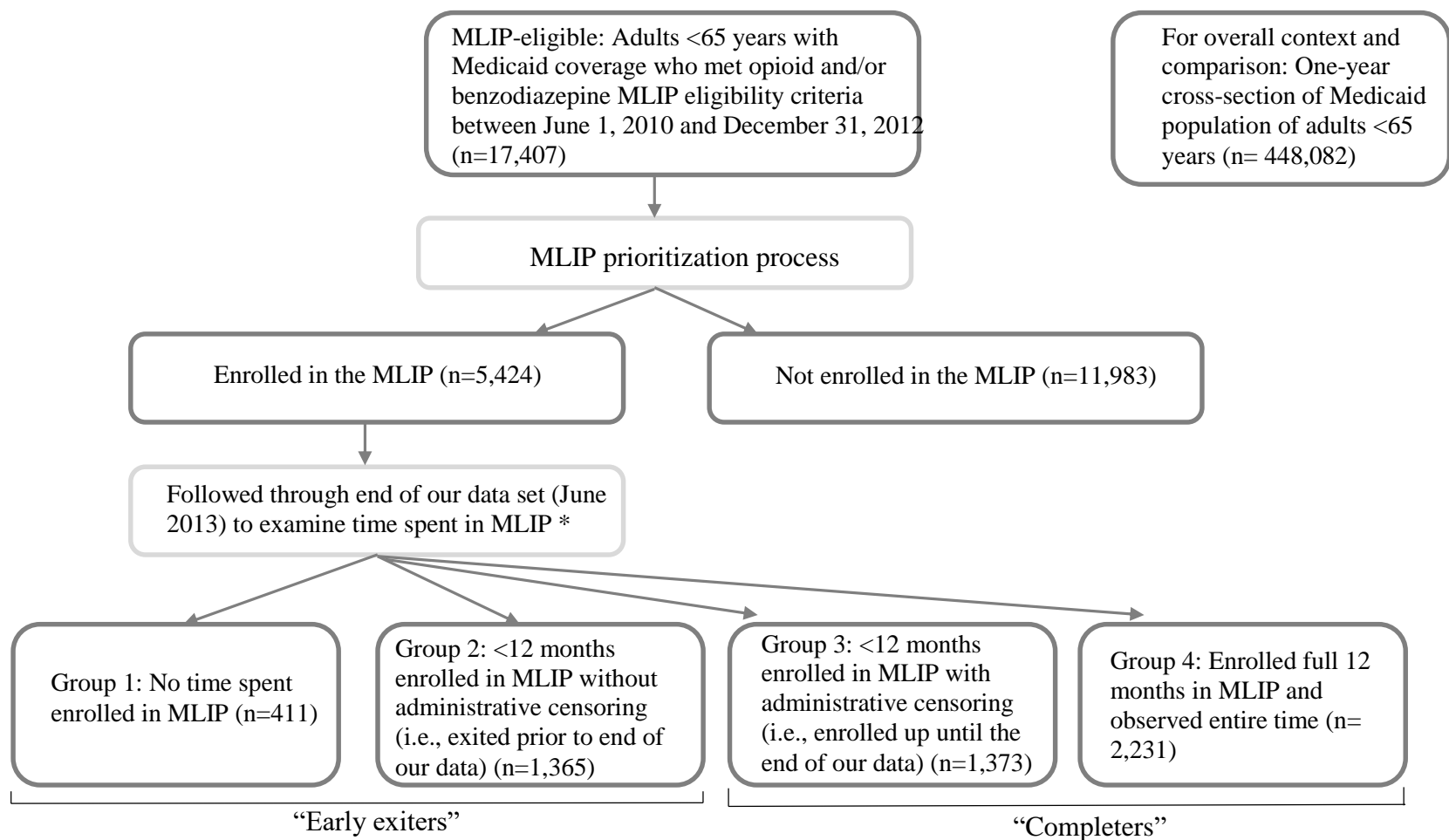
Note: Dark grey boxes represent groups compared. Light grey boxes represent processes. ***** 44 persons were enrolled in the MLIP for longer than a year and are not included in the analysis stratified by time spent in the MLIP.

Table 5.1 Demographic characteristics* of adults <65 years with Medicaid coverage overall and who met Medicaid Lock-in Program (MLIP) eligibility criteria from June 2010 through December 2012, stratified by enrollment in the MLIP and time spent in the MLIP (among those enrolled)

	General Medicaid adult population**	Medicaid population eligible for MLIP enrollment		MLIP-enrolled***			
	Medicaid beneficiary adult population <65 years (N= 448,082)	Not enrolled in the MLIP (n= 11,983)	Enrolled in the MLIP (n=5,424)	No time in MLIP (n=411)	<12 months in MLIP without administrative censoring (n=1,365)	<12 months in MLIP with administrative censoring (n=1,373)	Full 12 months in MLIP (n= 2,231)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age Group (years)							
18-24	130,467 (29.1)	1,048 (8.8)	597 (11.0)	71 (17.3)	197 (14.4)	124 (9.0)	199 (8.9)
25-29	62,764 (14.0)	1,404 (11.7)	890 (16.4)	86 (20.9)	286 (21.0)	191 (13.9)	322 (14.4)
30-34	51,173 (11.4)	1,638 (13.7)	993 (18.3)	79 (19.2)	306 (22.4)	238 (17.3)	363 (16.3)
35-39	44,446 (9.9)	1,523 (12.7)	826 (15.2)	73(17.8)	212 (15.5)	197 (14.4)	340 (15.2)
40-44	36,889 (8.2)	1,462 (12.2)	727 (13.4)	40 (9.7)	144 (10.6)	210 (15.3)	330 (14.8)
45-49	35,917 (8.0)	1,476 (12.3)	567 (10.5)	24 (5.8)	96 (7.0)	155 (11.3)	278 (12.5)
50-54	33,226 (7.4)	1,505 (12.6)	442 (8.2)	18 (4.4)	72 (5.3)	128 (9.3)	223 (10.0)
55-64	53,200 (11.9)	1,927 (16.1)	382 (7.0)	20 (4.9)	52 (3.8)	130 (9.5)	176 (7.9)
Age (years), mean (SD)	35.1 (13.5)	41.0 (11.9)	37.1 (10.6)	34.1 (10.0)	34.4 (9.7)	38.6 (10.8)	38.5 (10.7)
Gender							
Women	332,735 (74.3)	7,577 (63.2)	3,750 (69.1)	284 (69.1)	933 (68.4)	932 (67.9)	1,568 (70.3)
Men	115,347 (25.7)	4,406 (36.8)	1,674 (30.9)	127 (30.9)	432 (31.7)	441 (32.1)	663 (29.7)

Race							
White	235,845 (52.6)	8,980 (74.9)	4,155 (76.6)	349 (84.9)	1,131 (82.9)	996 (72.5)	1,644 (73.7)
Black	173,945 (38.8)	2,381 (19.9)	966 (17.8)	45 (11.0)	156 (11.4)	308 (22.4)	450 (20.2)
American Indian	8,917 (2.0)	275 (2.3)	169 (3.1)	7 (1.7)	45 (3.3)	36 (2.6)	80 (3.6)
Other (e.g., Asian, Pacific Islander)	4,339 (1.0)	26 (0.2)	13 (0.2)	2 (0.5)	3 (0.2)	2 (0.2)	6 (0.3)
Unreported	25,036 (5.6)	321 (2.7)	121 (2.2)	8 (2.0)	30 (2.2)	31 (2.3)	51 (2.3)
Urbanicity of county of residence †							
Counties in metro areas of ≥ 1 million population	109,402 (24.4)	2,718 (22.7)	1,399 (25.8)	114 (27.7)	362 (26.5)	361 (26.3)	553 (24.8)
Counties in metro areas of < 1 million population	197,021 (44.0)	5,550 (46.3)	2,457 (45.3)	190 (46.2)	580 (42.5)	606 (44.1)	1,059 (47.5)
Nonmetro, urban population of ≥ 20,000	74,873 (16.7)	2,081 (17.4)	891 (16.4)	64 (15.6)	218 (16.0)	241 (17.6)	358 (16.1)
Nonmetro, urban population of <20,000 or rural population	66,786 (14.9)	1,628 (13.6)	677 (12.5)	43 (10.5)	205 (15.0)	165 (12.0)	261 (11.7)
Overdose death rate in county of residence (per 100,000 py) ‡							
20.0-32.2	70,733 (15.8)	2,407 (20.1)	1,020 (18.8)	89 (21.7)	290 (21.3)	227 (16.5)	408 (18.3)
15.0-19.9	85,091 (19.0)	3,131 (26.1)	1,234 (22.8)	103 (25.1)	343 (25.1)	296 (21.6)	479 (21.5)
11.1-14.9	100,266 (22.4)	2,433 (20.3)	1,268 (23.4)	83 (20.2)	282 (20.7)	348 (25.4)	538 (24.1)
8.7-11.0	107,900 (24.1)	2,501 (20.9)	1,133 (20.9)	76 (18.5)	269 (19.7)	296 (21.6)	488 (21.9)
2.6-8.6	84,092 (18.8)	1,505 (12.6)	769 (14.2)	60 (14.6)	181 (13.3)	206 (15.0)	318 (14.3)
Aid category code §							
Aid to families with dependent children	212,931 (47.5)	5,809 (48.5)	3,298 (60.8)	335 (81.5)	1,072 (78.5)	725 (52.8)	1,144 (51.3)
Aid to disabled	162,792 (36.3)	5,793 (48.3)	1,956 (36.1)	44 (10.7)	226 (16.6)	617 (44.9)	1,048 (47.0)
Aid to pregnant women	44,714 (10.0)	282 (2.4)	142 (2.6)	29 (7.1)	59 (4.3)	22 (1.6)	31 (1.4)
Other (e.g., aid to blind)	27,645 (6.2)	99 (0.8)	28 (0.5)	3 (0.7)	8 (0.6)	9 (0.7)	8 (0.4)

Medicaid class code §

Categorically needy	369,806 (82.5)	10,904 (91.0)	5,084 (93.7)	344 (83.7)	1,213 (88.9)	1,321 (96.2)	2,164 (97.0)
Medically needy	19,509 (4.4)	1,015 (8.5)	337 (6.2)	65 (15.8)	152 (11.1)	52 (3.8)	67 (3.0)
Other (e.g., "qualified beneficiary" with Medicare & Medicaid benefits)	58,767 (13.1)	64 (0.5)	3 (0.1)	2 (0.5)	0	0	0

PY=person-years; SD= standard deviation

* Demographic characteristics assessed at time of first pharmacy claim between Oct 2009 and Sept 2010 for general Medicaid population and at time of first becoming eligible for MLIP for MLIP-eligible population.

** Cross-section of Medicaid population taken as beneficiaries ages 18-64 years who had at least one pharmacy claim between Oct 2009-Sept 2010.

*** 44 people were enrolled in the MLIP for >12 months and are not included in analyses stratified by time spent in the MLIP.

† 6 persons in the "not enrolled in the MLIP" group were missing county information.

‡ North Carolina has 100 counties. Counties were categorized in overdose rate quintiles (i.e., 20 counties per quintile). Rates are presented as deaths per 100,000 population per year.

§ The aid category codes and Medicaid class codes provide information on reasons people became eligible for Medicaid. Those who were classified as "categorically needy" met Medicaid income requirements under a specific aid category (e.g., families with children, disabled, etc.) to qualify. Those qualifying as "medically needy" satisfied Medicaid's categorical eligibility requirements (e.g., disability) but may have not satisfied financial eligibility requirements (i.e., income was too high). However, these individuals may have stilled qualified for Medicaid if they had significant medical expenses that reduced their income below a certain level, through "medically needy" programs.

Table 5.2 Controlled substance-related characteristics of adults <65 years who met Medicaid Lock-in Program (MLIP) eligibility criteria from June 2010 through December 2012, stratified by enrollment in the MLIP and time spent in the MLIP (among those enrolled)

	Medicaid population eligible for MLIP enrollment		MLIP-enrolled*			
	Not enrolled in the MLIP (n= 11,983)	**Enrolled in the MLIP (n=5,424)**	**No time in MLIP (n=411)**	**<12 months in MLIP without administrative censoring (n=1,365)**	**<12 months in MLIP with administrative censoring (n=1,373)**	**Full 12 months in MLIP (n= 2,231)**
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
*MLIP eligibility criteria met**						
Opioid criteria only met	11,197 (93.4)	5,260 (97.0)	403 (98.1)	1,327 (97.2)	1,325 (96.5)	2,162 (96.9)
Benzodiazepine criteria only met	755 (6.3)	139 (2.6)	6 (1.5)	32 (2.3)	42 (3.1)	58 (2.6)
Both opioid and benzodiazepine criteria met	31 (0.3)	25 (0.5)	2 (0.5)	6 (0.4)	6 (0.4)	11 (0.5)
Pharmacy utilization						
Obtained opioid and/or benzodiazepine prescriptions from >3 unique pharmacies when MLIP eligibility met	931 (7.8)	1,574 (29.0)	166 (40.4)	488 (35.8)	326 (23.7)	587 (26.3)
Medication-assisted treatment in past year						
Methadone treatment***	112 (0.9)	94 (1.7)	8 (2.0)	25 (1.8)	18 (1.3)	43 (1.9)

Buprenorphine prescription fill†	154 (1.3)	206 (3.8)	9 (2.2)	69 (5.1)	46 (3.4)	79 (3.5)

Overdose in past year

Any medication or drug-related‡	432 (3.6)	290 (5.4)	18 (4.4)	68 (5.0)	72 (5.2)	130 (5.8)
Opioid- or benzodiazepine-related§	188 (1.6)	125 (2.3)	10 (2.4)	27 (2.0)	26 (1.9)	61 (2.7)
Prescription opioid- or benzodiazepine-related^	163 (1.4)	110 (2.0)	8 (2.0)	24 (1.8)	21 (1.5)	56 (2.5)

* 44 people were enrolled in the MLIP for >12 months and are not included in analyses stratified by time spent in the MLIP.

** Captures MLIP criteria met in first 2-month period of becoming MLIP-eligible

*** Any mention of CPT code H0020, "Alcohol and/or drug services; methadone administration and/or service (provision of the drug by a licensed program)".

† Any prescription claim for a buprenorphine product indicated for use of opioid addiction treatment (i.e., medication assisted treatment).

‡ Any mention of the following ICD-9 diagnosis codes 960-979 or e-codes E850-E858, E950.0-E950.5, E962.0, E980.0-E980.5.

§ Any mention of the following ICD-9 diagnosis codes 965.00-965.09 (or 965.0), 969.4 or e-codes E850.0-E850.2.

^ Any mention of the following ICD-9 diagnosis codes 965.02, 965.09, 969.4 or e-codes E850.1-E850.2.

Table 5.3 Overall health care utilization and comorbid conditions * of adults <65 years who met Medicaid Lock-in Program (MLIP) eligibility criteria from June 2010 through December 2012, stratified by enrollment in the MLIP and time spent in the MLIP (among those enrolled)

	Medicaid population eligible for MLIP enrollment		MLP-enrolled**			
	Not enrolled in the MLIP (n= 11,983)	Enrolled in the MLIP (n=5,424)	No time in MLIP (n=411)	<12 months in MLIP without administrative censoring (n=1,365)	<12 months in MLIP with administrative censoring (n=1,373)	Full 12 months in MLIP (n= 2,231)
	Mean [25th, 50th, 75th percentiles]	Mean [25th, 50th, 75th percentiles]	Mean [25th, 50th, 75th percentiles]	Mean [25th, 50th, 75th percentiles]	Mean [25th, 50th, 75th percentiles]	Mean [25th, 50th, 75th percentiles]
Health care utilization in past year						
Emergency department visits	4.2 [1, 3, 5]	8.3 [2, 5, 11]	7.5 [2, 5, 10]	8.0 [3, 6, 11]	8.0 [2, 5, 10]	8.9 [2, 6, 11]
Inpatient admissions	1.0 [0, 0, 1]	1.1 [0, 1, 1]	0.9 [0, 0, 1]	0.9 [0, 0, 1]	1.2 [0, 1, 1]	1.2 [0, 1, 2]
Days with Medicaid coverage	308.7 [273, 365, 365]	310.1 [274, 365, 365]	252.7 [153, 273, 365]	282.9 [202, 335, 365]	319.4 [305, 365, 365]	331.2 [365, 365, 365]
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pain-related diagnoses in past year						
Any joint pain or arthritis***	9,620 (80.3)	4,608 (85.0)	316 (76.9)	1,087 (79.6)	1,193 (86.9)	1,972 (88.4)
Back pain***	7,498 (62.6)	4,219 (77.8)	307 (74.7)	1,029 (75.4)	1047 (76.3)	1,797 (80.6)
Neck pain***	3,247 (27.1)	1,919 (35.4)	112 (27.3)	443 (32.5)	496 (36.1)	852 (38.2)
Headache/migraine pain***	1,652 (13.8)	1,053 (19.4)	67 (16.3)	264 (19.3)	255 (18.6)	460 (20.6)

Fibromyalgia, chronic pain, or fatigue †	3,990 (33.3)	2,248 (41.5)	114 (27.7)	468 (34.3)	591 (43.0)	1,051 (47.1)
Rheumatoid arthritis or osteoarthritis ‡	2,091 (17.5)	1,074 (19.8)	47 (11.4)	195 (14.3)	303 (22.1)	519 (23.3)
Sickle cell §	87 (0.7)	84 (1.6)	0	7 (0.5)	28 (2.0)	49 (2.2)
Mental health and substance use-related diagnoses in past year						
Depression^	5,349 (44.6)	2,871 (52.9)	177 (43.1)	650 (47.6)	704 (51.3)	1,315 (58.9)
Bipolar disorder †	1479 (12.3)	932 (17.2)	48 (11.7)	188 (13.8)	221 (16.1)	469 (21.0)
Personality disorder †	230 (1.9)	175 (3.2)	7 (1.7)	29 (2.1)	36 (2.6)	99 (4.4)
Schizophrenia and other psychotic disorders †	482 (4.0)	169 (3.1)	5 (1.2)	25 (1.8)	52 (3.8)	84 (3.8)
Anxiety disorder †	3,017 (25.2)	1,946 (35.9)	113 (27.5)	430 (31.5)	522 (38.0)	862 (38.6)
Post-traumatic stress disorder †	444 (3.7)	319 (5.9)	17 (4.1)	59 (4.3)	76 (5.5)	164 (7.4)
Alcohol-related disorder #	795 (6.6)	347 (6.4)	19 (4.6)	78 (5.7)	94 (6.9)	152 (6.8)
Other substance-related disorder #	1,620 (13.5)	1,261 (23.3)	78 (19.0)	297 (21.8)	343 (25.0)	530 (23.8)
Other comorbid conditions in past year						
Mean Charlson co-morbidity index (SD) ~	1.68 (2.8)	0.79 (1.5)	0.47 (1.3)	0.59 (1.4)	0.91 (1.6)	0.90 (1.5)
Mean Charlson co-morbidity index without cancer (SD)	0.90 (1.6)	0.76 (1.4)	0.42 (1.1)	0.55 (1.2)	0.90 (1.6)	0.85 (1.4)

Cancer ∞	1,598 (13.3)	42 (0.8)	3 (0.7)	11 (0.8)	4 (0.3)	23 (1.0)
Congestive heart failure	531 (4.4)	195 (3.6)	6 (1.5)	36 (2.6)	58 (4.2)	94 (4.2)
Chronic obstructive pulmonary disease	2,744 (22.9)	1,219 (22.5)	55 (13.4)	208 (15.2)	365 (26.6)	581 (26.0)
Diabetes with complications	374 (3.1)	135 (2.5)	4 (1.0)	24 (1.8)	41 (3.0)	66 (3.0)
Diabetes without complications	1,886 (15.7)	682 (12.6)	31 (7.5)	117 (8.6)	205 (14.9)	322 (14.4)
Mild liver disease	640 (5.3)	284 (5.2)	13 (3.2)	61 (4.5)	71 (5.2)	135 (6.1)
Renal disease	364 (3.0)	122 (2.3)	6 (1.5)	18 (1.3)	37 (2.7)	60 (2.7)

SD= standard deviation

* Comorbid conditions and characteristics assessed in year prior to fully meeting MLIP eligibility criteria.

** 44 people were enrolled in the MLIP for >12 months and are not included in analyses stratified by time spent in the MLIP.

*** Pain categorizations used in previous research (Sullivan et al., 2008) and have been shown to be the most commonly reported chronic pain sites and reasons for long-term opioid use in a general medical population. Required any mention of specific ICD-9 diagnosis codes; see Sullivan et al. (2008) for additional details.[145]

† Centers for Medicare & Medicaid Services' (CMS) Chronic Conditions Data Warehouse definition used. Definition required at least 1 inpatient or 2 non-inpatient claims with specific ICD-9 diagnosis codes appearing more than once over a time span exceeding 30 days.[170]

‡ CMS Chronic Conditions Data Warehouse definition used with slight modification. Required at least 1 inpatient or 2 non-inpatient claims with specific ICD-9 diagnosis codes appearing more than once over a time span exceeding 30 days.[170]

§ Consistent with other studies (Reeves et al., 2014) and Agency for Healthcare Research and Quality's (AHRQ) Clinical Classification Software (CCS) definition, required at least 1 inpatient or 2 non-inpatient claims with specific ICD-9 diagnosis codes that appear more than once over a time span exceeding 30 days.[139,171]

^ CMS Chronic Conditions Data Warehouse definition used. Definition requires at least 1 inpatient, skilled nursing facility, home health agency, hospital outpatient, or service/carrier claims with specific ICD-9 diagnosis codes within 1 year.[170]

AHRQ's CCS definition used, which required at least 1 inpatient or 2 non-inpatient claims with the specific ICD-9 diagnosis codes that appear more than once over a time span exceeding 30 days.[139]

~ The Charlson Comorbidity Index (CCI) is a method of categorizing comorbidities based on ICD codes. Each comorbidity is associated with a weight (from 1 to 6), and weights are based on the adjusted risk of mortality or resource use. CCI scores are calculated by summing an individual's weights; a score of zero indicates no comorbidities were detected. We used Quan's enhanced CCI macro which looks at 17 comorbidities. An individual comorbidity was considered present if there was at least 1 inpatient or 2 non-inpatient claims with the specific ICD-9 diagnosis codes that appeared more than once over a time span exceeding 30 days. Select specific comorbidities are listed below the mean indices and definitions can be found in Quan et al. (2005).[154]

∞ Captures any malignancy, including lymphoma and leukemia, except malignant neoplasms of the skin.
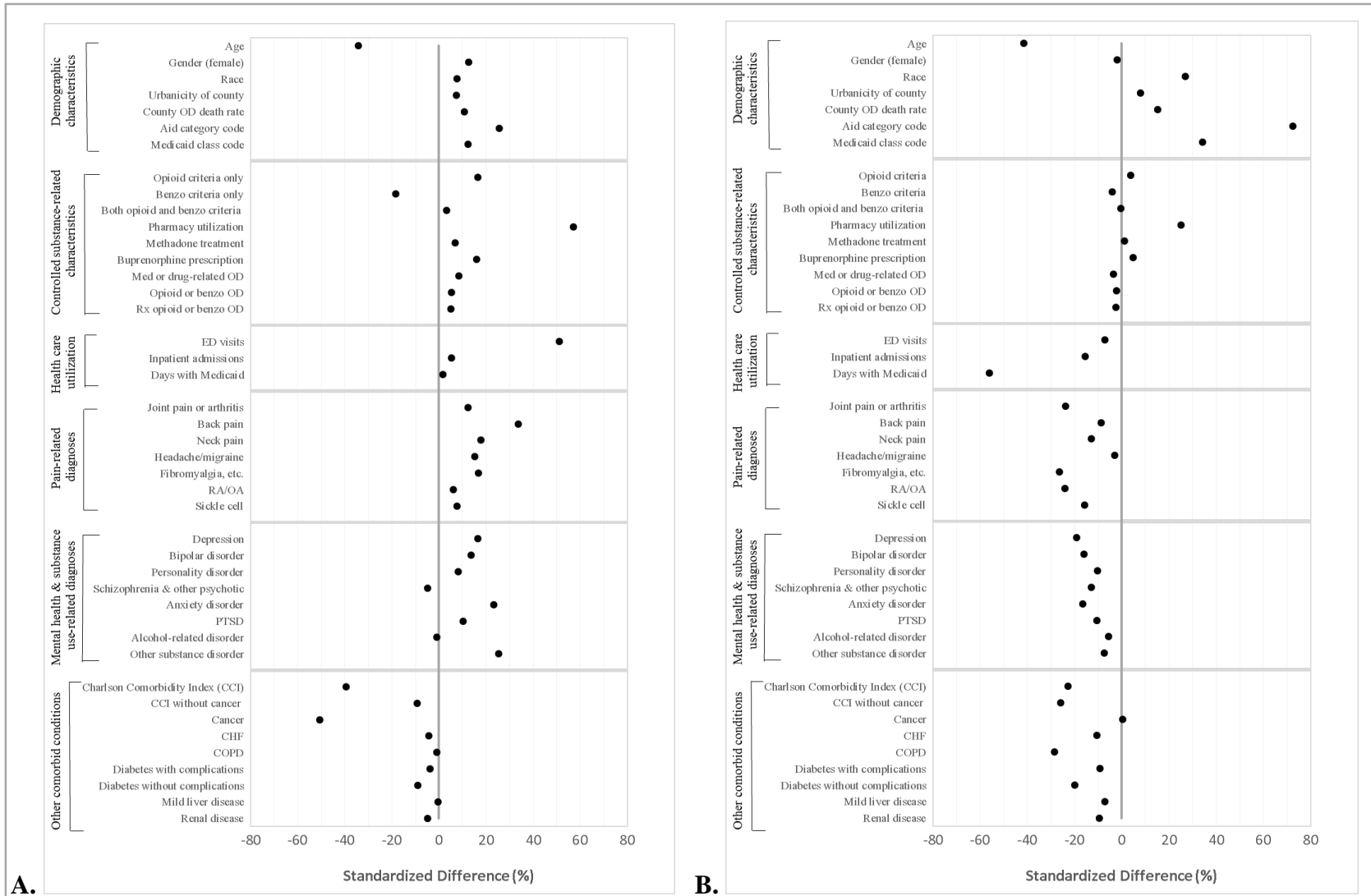
Figure 5.2 Standardized differences in characteristics* of beneficiaries who were enrolled vs. not enrolled (reference group) in the Medicaid Lock-in Program (MLIP) (Panel A) and among those enrolled, differences in characteristics between MLIP "early exiters" vs. "completers" (reference group) (Panel B)

* Additional variable details and definitions for demographic characteristics can be found in Table 5.1, for controlled substance-related characteristics in Table 5.2, and for all other variables in Table 5.3.

OD=overdose; benzo=benzodiazepine; rx=prescription; ED=emergency department; fibromyalgia, etc.= fibromyalgia, chronic pain, and fatigue; RA/OA=rheumatoid arthritis/osteoarthritis; PTSD=post-traumatic stress disorder; CCI=Charlson comorbidity index; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease

CHAPTER 6 – EVALUATING SHORT- AND LONG-TERM IMPACTS OF A MEDICAID "LOCK-IN" PROGRAM ON CONTROLLED SUBSTANCES DISPENSED TO BENEFICIARIES (MANUSCRIPT 2)

6.1 Overview

Background: Insurance-based "lock-in" programs (LIPs) have become a popular strategy to address controlled substance (CS) (e.g., opioid) misuse. However, little is known about their impacts. We examined changes in CS dispensing to beneficiaries in the 12-month North Carolina Medicaid LIP.

Methods: We analyzed Medicaid claims linked to Prescription Drug Monitoring Program (PDMP) records for beneficiaries enrolled in the LIP between October 2010 and September 2012 (n= 2,702). Outcomes of interest were 1) number of dispensed CS prescriptions and 2) morphine milligram equivalents (MME) of dispensed opioids while a) locked-in and b) in the year following release.

Results: Compared to a period of stable CS dispensed prior to LIP enrollment, numbers of dispensed CS during lock-in and post-release were lower (count difference per person-month: -0.05 (95% CI: -0.11, 0.01); -0.23 (95% CI: -0.31, -0.15), respectively). However, beneficiaries' average daily MMEs of opioids were elevated during both lock-in and post-release (daily mean difference per person: 18.7 (95% CI: 13.9, 23.6); 11.1 (95% CI: 5.1, 17.1), respectively). Stratification by payer source revealed increases in using non-Medicaid (e.g., out-of-pocket) payment during lock-in that persisted following release.

Conclusions: While the LIP reduced the number of CS dispensed, the program was also associated with increased acquisition of CS prescriptions using non-Medicaid payment. Moreover, beneficiaries acquired greater dosages of dispensed opioids from both Medicaid and non-Medicaid payment sources during lock-in and post-release. Refining LIPs to increase beneficiary access to substance use disorder screening and treatment services and provider use of PDMPs may address these important unintended consequences.

6.2 Introduction

Between 2000 and 2015, half a million Americans died from a drug overdose, and the majority of these deaths involved an opioid (57%).[1] The rapid escalation in opioid deaths during this period was due to multiple factors, one of which was that previous perceptions and cautions related to the risks and addictive potential of opioid prescription drugs were inappropriately dismissed, and opioid prescribing rapidly escalated.[172]

Several policies and programs have been implemented in an attempt to curb opioid misuse, abuse, and addiction. One strategy used by insurers across the U.S., and especially by Medicaid, is a "lock-in" program (LIP). LIPs are designed to identify beneficiaries demonstrating potential overutilization of opioids and other controlled substance (CS) prescription drugs (e.g., benzodiazepines) and to limit the beneficiaries' access, typically by requiring them to use a single prescriber and/or pharmacy to obtain CS for a specified period of time, such as 12 months.[33,34]

Because LIPs are designed primarily to reduce waste and abuse of CS prescriptions in healthcare systems, evaluations have largely been limited to understanding changes in

prescription utilization and cost savings to insurers.[34,35,43,46,48,66,67,72] However, studies to date have failed to provide a comprehensive picture of LIP impacts from a beneficiary perspective, including a clear understanding of short and long-term LIP impacts on beneficiaries' CS prescription regimens.

Our team has been evaluating North Carolina's (NC) Medicaid LIP with the goal of providing a more complete understanding of LIP impacts on beneficiaries [80,83]. However, analyses to date have been limited to the "lock-in" period, and focused mainly on numbers of dispensed CS during this period. While examining dispensed CS prescriptions can provide insight into overall prescription coordination within this population, understanding total dosages received helps us more closely assess beneficiary treatment regimens and the potency of all prescriptions acquired. Thus, the purpose of this study was to: 1) expand estimation of LIP effects by exploring sustained LIP effects in the year following release from the program, and 2) estimate both immediate and sustained LIP effects on the dosage of opioid prescriptions dispensed to beneficiaries, in terms of average daily morphine milligram equivalents (MMEs).

6.3 Methods

Study design overview

Using an observational prospective cohort study design, we established and followed a cohort of independently living adults (e.g., excluding those living in residential facilities) between the ages of 18 and 64 who were enrolled in the NC Medicaid LIP between October 2010 and September 2012. In order to obtain a more complete picture of LIP effects, we used NC Medicaid claims linked to records from the NC Controlled Substance Reporting System

85

(CSRS), the state's Prescription Drug Monitoring Program (PDMP). To understand sustained LIP influence, we included up to 12 months of person-time on beneficiaries following release from the program. We estimated program effects while locked-in and following LIP release on numbers of dispensed CS per person-month and average daily MMEs of dispensed opioids per person.

North Carolina's Medicaid LIP

The NC Medicaid LIP was first implemented in October 2010.[173] Medicaid beneficiaries were eligible for the LIP if they met any of the following criteria within a two consecutive calendar month period: if they filled (1) more than six opioid prescriptions, (2) more than six benzodiazepine prescriptions, or (3) either opioid or benzodiazepine prescriptions that were written by more than three different prescribers.[173] Each month, LIP-eligible beneficiaries, as determined from Medicaid prescription dispensing information for the previous two months, were prioritized for LIP enrollment using a proprietary algorithm combined with a review process by pharmacists. Based on this prioritization, approximately 200 of the highest-ranking beneficiaries were selected for LIP enrollment each month. Beneficiaries were notified of their selection for program enrollment and that LIP enrollment restricted them to using one prescriber and one pharmacy location to obtain prescriptions categorized as opioids or benzodiazepines for a one-year period. Beneficiaries were given 30 days to choose a preferred prescriber and pharmacy before restrictions began. If they did not choose a preferred prescriber and pharmacy, they were assigned one of each. Additional details of the implementation and administration of NC's Medicaid LIP have been previously provided.[174]

Linked Medicaid claims and Prescription Drug Monitoring Program data

Our research team linked NC Medicaid claims to records from the NC CSRS. Linked data for the period of October 2009 through June 2013 were obtained for beneficiaries enrolled in the LIP between October 2010 and September 2012. NC Medicaid claims included beneficiaries' demographics, periods of Medicaid enrollment, adjudicated pharmacy and medical claims, and assigned LIP enrollment and release dates. NC CSRS records included data on all CS (schedules II-V) dispensed to LIP beneficiaries, regardless of source of payment (e.g., Medicaid-reimbursed, out-of-pocket). Data were linked manually using a standardized protocol that included deterministically matching records based on the first five letters of the beneficiary's last name, date of birth within six months, and the first two or three letters of the beneficiary's first name. The protocol included rigorous data integrity checks and steps to help ensure that all of a given beneficiaries' records were included and that issues such as minor misspellings or use of a common nickname would not prevent linkage. Once linked, dummy identifiers were assigned to all beneficiaries and identifying information was deleted. Additional details on the linkage have been previously documented.[83]

Study subjects and design details

To estimate the association between LIP-related periods and numbers of CS dispensed per person-month, beneficiaries in our cohort were followed from the first day of receiving any CS prescription (i.e., opioid or benzodiazepine) on or after October 1, 2009, throughout their period of lock-in, and up to one year following program release or until June 30, 2013, whichever came first. To estimate the association between LIP-related periods and average daily MMEs of dispensed prescription opioids per person, beneficiaries were followed in the same

manner, except that their start of follow-up was the first day of receiving any opioid prescription, as opposed to any opioid or benzodiazepine prescription.

To avoid conflating program effects for those who remained continuously enrolled in the LIP and those who exited the LIP prior to completion,[174] we restricted this analysis to those who remained in the LIP for a full 12 months or were administratively censored in June 2013, the last month for which we had data. We defined continuous enrollment as no more than a 7-day gap in coverage. These beneficiaries constituted 62% of all beneficiaries ages 18-64 years with an independent living arrangement who were ever enrolled in the LIP between October 2010 and September 2012. There were no requirements regarding continuous Medicaid coverage in the time prior to LIP enrollment or in the year after LIP release. However, previous analyses indicated that those with continuous coverage while enrolled in the LIP had, on average, close to complete Medicaid coverage prior to enrollment as well.[174]

"Lock-in" status over time

To examine changes in the numbers of CS dispensed per person-month and average daily MMEs of dispensed opioids per person, we divided time into four segments: two pre-enrollment periods (>6 months pre-enrollment, or "pre-spike," and 0-6 months pre-enrollment, or "spike"), a 12-month program period ("lock-in"), and a period (up to 12 months) after program release ("post-release"). Descriptive analyses revealed a specific period with large spikes in numbers and dosages of CS dispensed, in the months just prior to program enrollment. This spike period precipitated LIP enrollment for many beneficiaries. During this period, a sudden escalation was met by a similar de-escalation just prior to LIP enrollment, resulting in dispensing that appeared to largely return to pre-spike levels just prior to actual enrollment (Figure 6). Moreover,

additional analyses revealed that this pattern of escalation, triggering of LIP criteria, and a nearly equal de-escalation was not unique to the LIP-enrolled population. It also occurred in Medicaid beneficiaries who were never enrolled in the LIP but met the LIP eligibility criteria. While this spike period reveals critical information regarding the average CS utilization trajectory leading to eligibility for the LIP, this volatile period of utilization is likely not the most appropriate reference period for LIP effect estimation. Rather, understanding the extent to which the LIP was associated with CS utilization during and upon release, as compared to a more stable utilization period prior to program enrollment provides a more suitable comparison. Therefore, we stratified pre-enrollment time into pre-spike and spike periods and focused our LIP effect estimation on dispensing during lock-in and post-release periods as compared to the pre-spike period.

Outcome measures

We examined monthly numbers of dispensed CS prescriptions by payer source—Medicaid-reimbursed, not Medicaid-reimbursed (e.g., out-of-pocket), and those paid for using any source. In addition to examining LIP effects on numbers of CS obtained, we also quantified the effect on the average dosage of dispensed opioid prescriptions. Average daily MME is a research measure commonly used to compare diverse opioid medication regimens using a standardized unit, morphine equivalents.[109] To calculate the average daily MME of a given opioid prescription, we multiplied the drug's strength by the quantity received and a medication-specific MME conversion factor and divided by the days' supply received.[114] The average daily MME for each prescription was then applied to all days for which the prescription was active (i.e., all days in which the prescription was to be taken, according to the days' supply). If a

beneficiary had more than one opioid prescription active on a given day, the MMEs for that day were summed. Average daily MMEs were also stratified by source of payment.

Similar dosing equivalencies for benzodiazepines are less evidence-based, poorly described, and often based on expert opinion. Moreover, the majority of CS prescriptions received by LIP-enrolled beneficiaries consisted of opioids (approximately 75-80%); therefore, we did not calculate similar dosage estimates for benzodiazepines.

Covariates

To elucidate potential sources of confounding that could impact our estimation of LIP effects on CS prescription utilization, we developed a conceptual figure based on the best available literature and our understanding of factors affecting LIP exposure and the outcome measures of interest. The figure included demographic, Medicaid eligibility-related, and clinical characteristics, which we evaluated as sources of confounding. Demographic and Medicaid-related characteristics were assessed at the time of LIP enrollment and included age, sex, race, urbanicity of the beneficiary's county of residence, overdose death rate in the beneficiary's county of residence, Medicaid aid category, and Medicaid class code. Clinical characteristics were assessed using a one-year lookback period from the date of LIP enrollment and included history of alcohol or other substance use-related disorders, history of medication-assisted treatment for opioid addiction, history of an overdose event, number of unique pharmacies visited, number of emergency department visits, number of inpatient admissions, history of specific pain-related diagnoses (e.g., arthritis, back, neck, headache/migraine, fibromyalgia, sickle cell), history of specific mental health-related diagnoses (e.g., depression, anxiety, bipolar, schizophrenia), and Charlson comorbidity index. Specific information on variable categories and

claims-related codes used to define clinical characteristics, as well as information on the prevalence of these characteristics in the LIP population, can be found in Chapter 5.[174]

To help control for confounding by time due to changes in awareness and CS prescribing culture and use during this time, we generated temporal trend measures that allowed us to control for changes in outcomes occurring over calendar time. We generated these measures from temporal trends in outcome measures in the population of Medicaid beneficiaries who were eligible to enter the LIP, but were never enrolled. These temporal trend measures were included in all models. For further details, see Appendix C.

Statistical Analyses

To visualize changes in the outcomes across pre-spike, spike, lock-in, and post-release periods, we plotted outcome means across these LIP-related time periods and according to payer source. To further descriptively examine and compare outcome measures over time, we calculated crude means of average daily MMEs per dispensed opioid per person by LIP-related time period and payer source.

We used generalized estimating equations (GEE) to estimate measures of association between LIP-related time periods (compared to the pre-spike referent period) and the average number of CS prescriptions dispensed per person-month and average daily MMEs of dispensed opioids per person. To examine changes in numbers of CS dispensed per person-month, we used both linear-Poisson and log-Poisson GEE models to estimate count differences and count ratios, respectively, with 95% confidence intervals (95% CI). A linear regression GEE (identity link,

Gaussian residual distribution) was used to estimate changes in average daily MMEs per person while locked-in and in the year post-release, as compared to the pre-spike period.

All models were specified with an exchangeable correlation matrix and used restricted cubic spline terms with five knots to adjust for temporal trend. For each model, we assessed the impact of confounding by including each potential confounder described above and examining measures of association for meaningful changes, defined as more than a 10% change in the beta estimates for measures of association. However, we observed no meaningful changes; therefore, these variables were not included in final models. Temporal trend measures described above were included in all models, including those in which we assessed confounding.

This study was approved by the University of North Carolina at Chapel Hill's Institutional Review Board.

6.4 Results

Between October 2010 and September 2012, 2,702 beneficiaries were enrolled in the LIP and remained enrolled in the LIP for a full one-year period (or remained continuously enrolled prior to being administratively censored in June 2013). As previously described,[174] beneficiaries were largely white (74%), female (70%), and had a mean age of 39 years. Half received Medicaid due to a disability, and they exhibited a high prevalence of pain and mental health-related diagnoses (e.g., more than half had a diagnosis of depression) in the year prior to LIP enrollment.

Pre-modeling results

Figure 6 displays crude means of monthly CS dispensed per person and average daily MMEs dispensed per person across LIP-related time (i.e., months/days from LIP enrollment) and by prescription payment source. The overall pattern in the mean numbers of all CS dispensed, paid for using any payment source, indicated a stable mean just over 2 prescriptions per month in the pre-spike period. This more than doubled to 5.2 prescriptions per month at the peak of the spike period, followed by a sudden decline just prior to LIP enrollment. There was with a slight decline while locked-in, and the mean post-release was similar to the pre-spike mean.

Crude means of average daily MMEs across program time revealed a similar pattern in terms of the spike and general stabilization of means during lock-in (Figure 6b). However, the pattern was dissimilar in that mean average daily MMEs increased across both pre-spike and post-release periods.

When stratified by payment source, crude means indicated an increase in the proportion of dispensed CS obtained through non-Medicaid sources while locked-in, which then largely, although not completely, reverted to pre-spike levels in the post-release period. However, for mean average daily MMEs, the increase in using non-Medicaid payment sources did not appear to revert to pre-spike levels in the post-release period.

Crude means of average daily MMEs per dispensed opioid per person from all payer sources indicated a steady increase in the mean across LIP-related periods (Table 6.1). However, stable medians suggested the mean increase was largely driven by a smaller subset of beneficiaries at the upper end of the distribution. Stratification by payment source revealed a

similar finding for non-Medicaid reimbursed opioids, in that a substantial increase in the mean was observed post-release while the median remained similar to other LIP-related periods. Finally, results for Medicaid-reimbursed opioids indicated an upward shift in the mean and median while enrolled in the lock-in.

Frequency and dosage of dispensed CS

Controlling for temporal trend in dispensed CS prescriptions, numbers of CS dispensed per person-month during lock-in and post-release were slightly lower than the pre-spike period (count difference per person-month: -0.05; 95% CI: -0.11, 0.01 and -0.23; 95% CI: -0.31, -0.15, respectively) (Table 6.2). Stratification by payer source revealed that large decreases in Medicaid-reimbursed prescriptions during lock-in and post-release were considerably offset by increases in non-Medicaid-reimbursed prescriptions during these periods. For example, compared to the pre-spike period, there were 0.61 (95% CI: -0.66, -0.55) and 0.38 (95% CI: -0.45, -0.31) fewer Medicaid-reimbursed prescriptions per person-month during lock-in and post-release, respectively. However, non-Medicaid-reimbursed prescriptions increased by 0.56 (95% CI: 0.52, 0.59) and 0.12 (95% CI: 0.08, 0.16) per person-month during lock-in and post-release, respectively. Similar patterns were observed in analyses restricted to opioids alone.

The average daily MME of opioids dispensed to beneficiaries was elevated during lock-in and post-release relative to pre-spike (daily mean difference per person: 18.7; 95% CI: 13.9, 23.6 and 11.1; 95% CI: 5.1, 17.1, respectively) (Table 6.3). Similar to dispensed CS, there were notable increases in reimbursement using non-Medicaid payment sources. Compared to the pre-spike period, 6.6 (95% CI: 4.8, 8.5) more average daily MMEs per person were purchased using non-Medicaid payment during lock-in and 6.2 (95% CI: 3.7, 8.6) more post-release.

94

6.5 Discussion

Key Findings

Consistent with previous research, we found that from an insurance-based perspective, LIPs appear to reduce CS prescriptions dispensed to beneficiaries enrolled in a state's Medicaid LIP. [34,35,46,48,66,67,72,83] This paper provides the first evidence that such reductions, although somewhat attenuated, persist in the year following disenrollment. For example, the average number of Medicaid-reimbursed CS dispensed per person-month was 31% lower during lock-in and 18% lower post-release, as compared to a stable period of dispensing prior to lock-in.

A strength of this study was access to information on prescriptions obtained through Medicaid and non-Medicaid payment sources, which revealed insights on intended and unintended consequences of the LIP. We found that while CS dispensing decreased overall, beneficiaries acquired more CS prescriptions outside of the Medicaid payment system while locked-in, compared to prior to LIP enrollment. The increased acquisition of CS from non-Medicaid sources persisted following program release. Concerns about increased acquisition of CS from non-Medicaid sources during lock-in have previously been noted;[83] however, this is the first study to indicate that these effects persist post-release.

We also found that beneficiaries received larger dosages of opioids in terms of average daily MMEs, during lock-in and post-release, regardless of payment source. The percent of average daily MMEs dispensed while locked-in increased by approximately 28% compared to the pre-enrollment (and pre-spike) period, and by about 17% post-release. While the majority of average daily MMEs were acquired through Medicaid payment, there were large increases in average daily MMEs obtained outside of the Medicaid payment system during these periods.

Approximately 12% of all average daily MMEs were paid for using non-Medicaid sources prior to enrollment, which increased to roughly 20% during lock-in and post-release.

The overall decline in numbers of dispensed CS and opioids and parallel increases in average daily MMEs suggests that opioids acquired during LIP and following release were characterized by greater average daily MMEs per prescription, relative to those obtained prior to the LIP. Descriptive analyses supported this finding but also revealed that increases may have been driven by select beneficiaries at the upper end of the dosage per prescription distribution.

From an insurance-based perspective, the increase in average daily MMEs per Medicaid-reimbursed opioid during lock-in could signal improved care coordination for some beneficiaries. In other words, LIP restrictions may have encouraged lock-in providers to more carefully assess beneficiaries' prescriptions regimens, reducing numbers of prescriptions (e.g., continuous 30-day prescriptions rather than multiple shorter-term prescriptions), while not reducing overall MMEs. Moreover, overall increases in MMEs dispensed to certain beneficiaries during lock-in and following release could indicate a natural progression of opioid tolerance in a population with a high prevalence of chronic pain. However, this increase may also indicate increases in average overdose risk for this population. Given that research suggests a dose-dependent relationship between average daily MMEs and opioid overdose risk,[110-112] future studies should explore potential changes in overdose risk across LIP-related periods.

Our finding that average daily MMEs per opioid obtained outside of the Medicaid system increased post-release may signal that some beneficiaries began acquiring more potent opioids outside of the purview of the Medicaid system following release from the program. Future research exploring heterogeneity underlying these population-level averages may help further disentangle subgroups experiencing potential unintended LIP effects.

Implications for LIP designs and policies

Our findings of LIP impacts on CS prescription measures provide key indications for intervention and LIP improvements. First, our finding that a substantial proportion of beneficiaries' average daily MMEs were obtained outside of the Medicaid payment system highlights the need for increased use of PDMPs. We lack data on how often NC Medicaid LIP providers, specifically, accessed the CSRS during this time. However, a 2012 evaluation of the CSRS indicated that prescribers and pharmacists used the CSRS less than 6% of the time that a CS was either prescribed or dispensed,[107] suggesting a missed opportunity to provide better informed care.

Second, given our finding of increased acquisition of MME dosages during lock-in and findings from previous analyses indicating that nearly a quarter of LIP enrollees had a diagnosis of a substance use-related disorder in the year prior to enrollment,[174] further research is needed on access to substance use disorder treatment, such as medication-assisted therapy, prior to, during, and following LIP release. If found to be underutilized, providing opportunities to discuss substance use behaviors (e.g., motivational interviewing) with LIP enrollees, a strategy that has been included in previous LIP models,[68] and ensuring access to substance use disorder treatment could potentially improve care and health outcomes.

Finally, our findings indicate that beneficiary behavior changes occurring during lock-in tend to persist following program release. Investment in a more comprehensive LIP model could produce benefits realized by both beneficiaries and insurers that are not limited to the one-year lock-in period. In addition to the elements discussed above, LIP models that incorporate case managers to help manage the complex and unique needs [174] of LIP enrollees (e.g., through

connection to alternate pain therapy services, mental health disorder treatment) may produce improved outcomes.[68]

Limitations

Our results should be viewed in light of three main limitations. First, we did not have linked claims-CSRS data on persons who were never enrolled in the LIP. While this group would have been useful as a control, we compensated by incorporating a novel method to control for changes in secular trend over time using Medicaid claims data from those eligible but never enrolled in the LIP.

Second, while the CSRS database captures almost all CS dispensed to these beneficiaries, there are some gaps in understanding beneficiaries' complete CS use. We do not have information on CS prescriptions acquired across state lines or from pharmacies located on military bases or veterans' administration hospitals, or CS that beneficiaries obtained through illicit sources (diversion). If these CS acquisitions increased during lock-in and post-release, our measures of association would be underestimated.

Finally, administrative censoring resulted in loss of follow-up in the one-year post-release period. It is possible that losses to follow-up were related to our outcome measures and could have introduced some bias when estimating measures of association involving the post-release period.

Conclusions

NC's Medicaid LIP reduced overall numbers of CS prescriptions dispensed during lock-in, and this reduction was sustained in the year following program release. However, the LIP was associated with acquiring a greater proportion of CS prescriptions using non-Medicaid payment sources both during lock-in and post-release. Moreover, beneficiaries acquired greater dosages of

dispensed opioids, in terms of average daily MMEs, from both Medicaid and non-Medicaid payment sources, both during lock-in and post-release. Refining LIPs to increase provider utilization of PDMP data, ensure access to substance use disorder treatment services, and incorporate complementary beneficiary support services may help address important unintended consequences and increase the overall utility of these programs. Future research is needed as to the short- and long-term impacts of alternate LIP designs and more comprehensive LIP models, incorporating measures that assess program impacts from both insurer and beneficiary perspectives. Additionally, future research exploring the potential heterogeneity underlying average population effects may help further refine and target LIPs to those most likely to benefit.
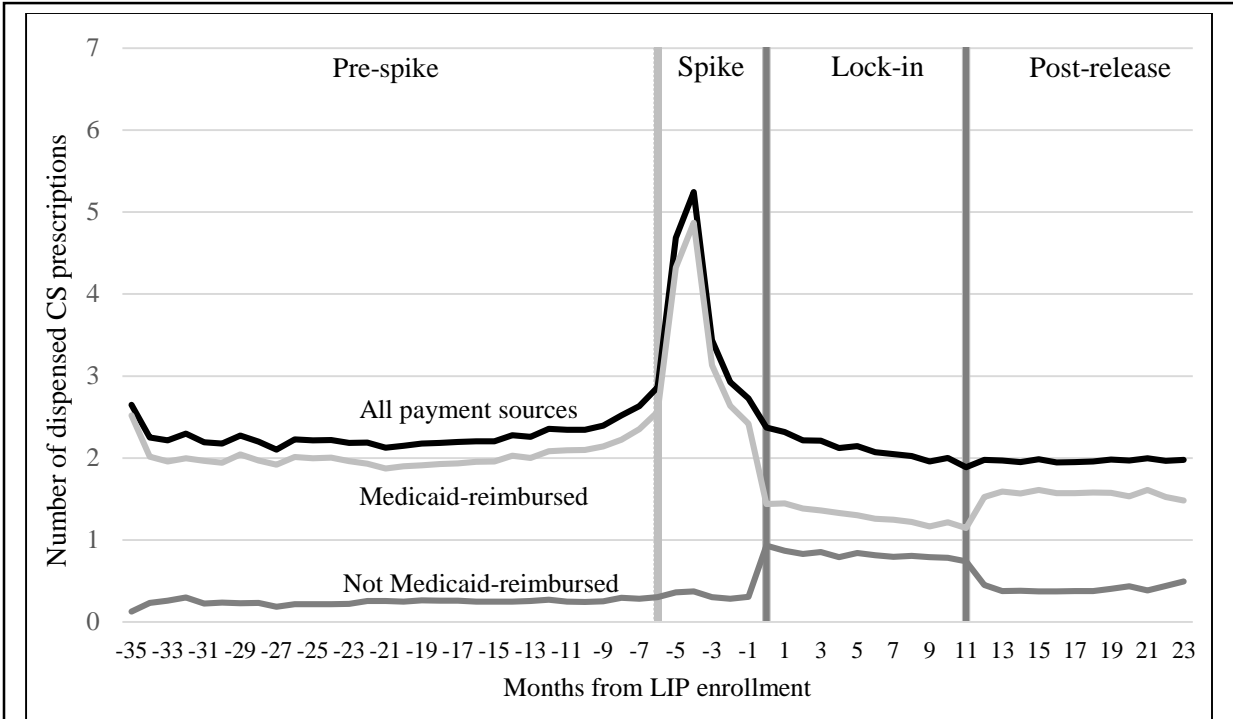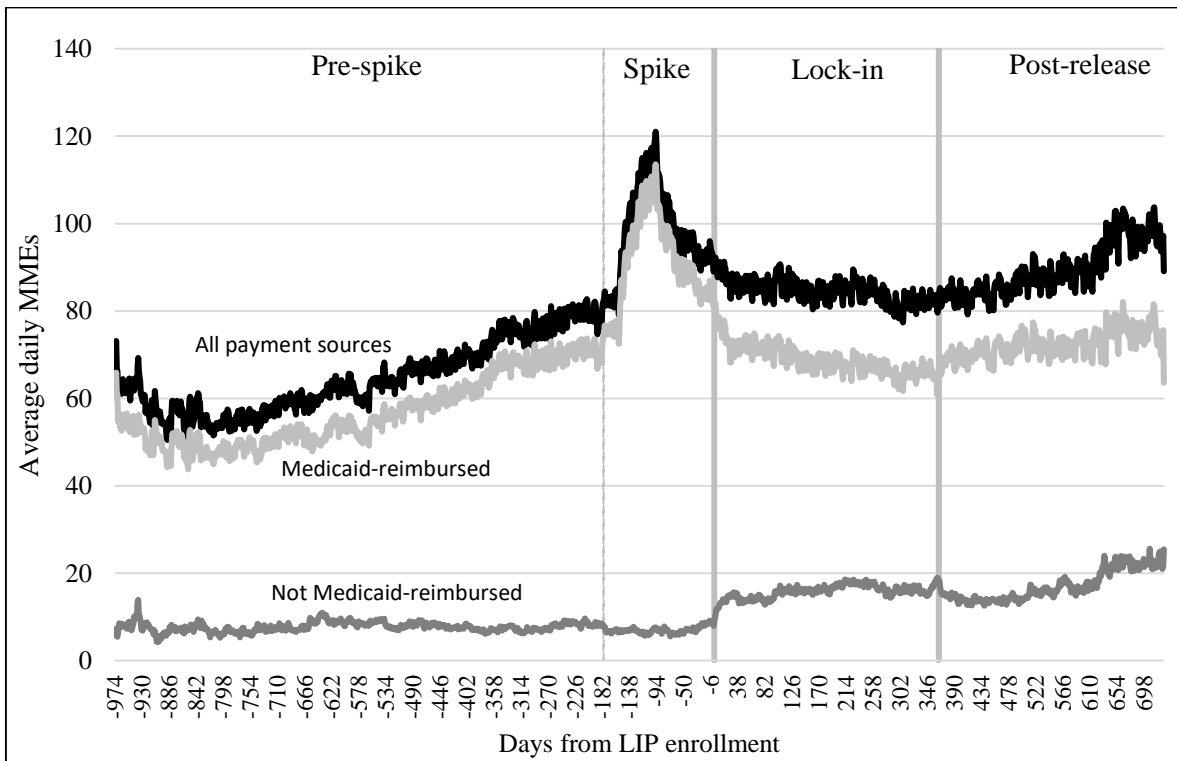
Figure 6. Average number of dispensed controlled substance (CS) prescriptions per person per month^ (Panel A) and average daily morphine milligram equivalents (MMEs) of dispensed opioid prescriptions (Panel B) per person across pre-spike, spike, lock-in, and post-release

periods* among North Carolina Medicaid "lock-in" program enrollees (n=2702), October 2009-June 2013

^ Includes CS prescriptions regulated by the lock-in program (LIP), specifically opioids and benzodiazepines
*Pre-spike period= more than 6 months prior to LIP enrollment; Spike period= 0-6 months prior to LIP enrollment; lock-in period= months enrolled in the LIP (up to 12 months); Post-release period= months after disenrollment from the LIP (up to 12 months following release)

Table 6.1 Means of average daily morphine milligram equivalents (MMEs) per dispensed opioid prescription per person among North Carolina Medicaid "lock-in" program (LIP) enrollees (n=2,702) by LIP-related time period[#] and payer source, October 2009-June 2013

Period[#]	All payer sources	Medicaid-reimbursed	Not Medicaid-reimbursed
	Mean (25th, 50th, 75th percentile)		
Pre-spike	58 (33, 44, 63)	58 (32, 44, 62)	58 (30, 43, 64)
Spike	62 (36, 48, 69)	62 (36, 48, 69)	59 (30, 45, 64)
Lock-in	67 (34, 47, 77)	75 (34, 55, 94)	55 (31, 41, 60)
Post-release	69 (32, 46, 83)	70 (31, 46, 86)	68 (30, 45, 75)

Pre-spike period= more than 6 months prior to LIP enrollment; Spike period= 0-6 months prior to LIP enrollment; Lock-in period= months enrolled in the LIP (up to 12 months); Post-release period= months after disenrollment from the LIP (up to 12 months following release)

Table 6.2 Means, count differences, and count ratios of monthly numbers of controlled substance prescriptions[§] dispensed to North Carolina Medicaid "lock-in" program (LIP) enrollees (n=2,702) by payer source and LIP-related time period[#], October 2009-June 2013

Period[#]	All payer sources			Medicaid-reimbursed			Not Medicaid-reimbursed		
	Model-estimated mean (95% CI)^	Count difference (95% CI)*	Count ratio (95% CI)*	Model-estimated mean (95% CI)^	Count difference (95% CI)*	Count ratio (95% CI)*	Model-estimated mean (95% CI)^	Count difference (95% CI)*	Count ratio (95% CI)*
Pre-spike	2.30 (2.24, 2.35)	Ref	Ref	2.01 (1.96, 2.05)	Ref	Ref	0.28 (0.26, 0.29)	Ref	Ref
Spike	3.65 (3.60, 3.70)	1.41 (1.36, 1.47)	1.63 (1.60, 1.67)	3.32 (3.28, 3.37)	1.37 (1.32, 1.42)	1.71 (1.75, 1.83)	0.32 (0.30, 0.35)	0.05 (0.03, 0.07)	1.20 (1.12, 1.29)
Lock-in	2.11 (2.06, 2.16)	-0.05 (-0.11, 0.01)	0.98 (0.95, 1.01)	1.29 (1.25, 1.34)	-0.61 (-0.66, -0.55)	0.69 (0.67, 0.71)	0.82 (0.79, 0.86)	0.56 (0.52, 0.59)	3.16 (2.92, 3.42)
Post-release	1.87 (1.81, 1.93)	-0.23 (-0.31, -0.15)	0.90 (0.86, 0.93)	1.47 (1.42, 1.52)	-0.38 (-0.45, -0.31)	0.82 (0.78, 0.85)	0.39 (0.36, 0.42)	0.12 (0.08, 0.16)	1.56 (1.41, 1.73)

§ Includes controlled substance prescriptions regulated by the LIP, specifically opioids and benzodiazepines
# Pre-spike period= more than 6 months prior to LIP enrollment; Spike period= 0-6 months prior to LIP enrollment; Lock-in period= months enrolled in the LIP (up to 12 months); Post-release period= months after disenrollment from the LIP (up to 12 months following release)
^ Estimated with linear Poisson GEE model, used average value of secular trend variable for each LIP time period
* Estimated with GEE model, adjusted for secular trend

Table 6.3 Means and changes in average daily morphine milligram equivalents (MME) of opioid prescriptions dispensed to North Carolina Medicaid "lock-in" program (LIP) enrollees (n=2,702) by payer source and LIP-related time period[#], October 2009-June 2013

Period[#]	All payer sources		Medicaid-reimbursed		Not Medicaid-reimbursed	
	Model-estimated mean (95% CI)^	Mean difference (95% CI)*	Model-estimated mean (95% CI)^	Mean difference (95% CI)*	Model-estimated mean (95% CI)^	Mean difference (95% CI)*
Pre-spike	66.2 (60.4, 72.0)	Ref	58.0 (52.5, 63.6)	Ref	8.2 (7.0, 9.3)	Ref
Spike	98.2 (91.7, 104.7)	32.3 (28.4, 36.1)	91.2 (84.9, 97.5)	34.2 (30.4, 38.0)	7.0 (6.1, 7.8)	-1.9 (-3.2, -0.7)
Lock-in	84.6 (79.0, 90.1)	18.7 (13.9, 23.6)	68.8 (63.7, 74.0)	12.1 (7.4, 16.8)	15.7 (14.1, 17.4)	6.6 (4.8, 8.5)
Post-release	77.4 (71.6, 83.3)	11.1 (5.1, 17.1)	62.0 (56.9, 67.1)	5.0 (-0.9, 10.8)	15.4 (12.8, 18.1)	6.2 (3.7, 8.6)

Pre-spike period= more than 6 months prior to LIP enrollment; Spike period= 0-6 months prior to LIP enrollment; Lock-in period= months enrolled in the LIP (up to 12 months); Post-release period= months after disenrollment from the LIP (up to 12 months following release)

^ Estimated with GEE model, used average value of secular trend variables for each LIP time period

* Estimated with GEE model, adjusted for secular trend

CHAPTER 7 – TRAJECTORIES OF DISPENSED PRESCRIPTION OPIOIDS AMONG BENEFICIARIES ENROLLED IN A MEDICAID CONTROLLED SUBSTANCE "LOCK-IN" PROGRAM (MANUSCRIPT 3)

7.1 Overview

Background: "Lock-in" programs (LIPs) are used by health insurers to address potential opioid and substance misuse among beneficiary populations. However, little is known about whether the effects of LIPs on beneficiaries' opioid utilization trajectories are heterogeneous across subpopulations.

Aims: (1) To examine heterogeneity in trajectories of dispensed opioids (in terms of average daily morphine milligram equivalents (MMEs)) over time: prior to, during, and following release from a LIP; and (2) to assess associations between trajectory patterns and key beneficiary characteristics.

Methods: Medicaid claims were linked to Prescription Drug Monitoring Program records for a cohort of beneficiaries enrolled in the North Carolina Medicaid LIP (n=2,701). Using latent class growth analyses, we estimated trajectories of average daily MMEs of opioids dispensed to beneficiaries across specific time periods of interest.

Results: Five trajectory patterns appeared to sufficiently describe underlying heterogeneity. All patterns demonstrated a spike in MMEs in the six months prior to lock-in, which appeared to trigger LIP enrollment. Starting values and slopes varied across the five trajectory groups, which followed these overall patterns: (1) start at a high level of MMEs, end at a high level of MMEs (13.1% of the cohort); (2) start medium, end medium (13.2%); (3) start medium, end low

105

(21.5%); (4) start low, end medium (22.6%); and (5) start low, end low (29.6%). We observed strong associations between patterns and beneficiaries' demographics, substance use-related characteristics, comorbid conditions, and overall healthcare utilization.

Conclusions: In its current form, the Medicaid "lock-in" program (LIP) appeared to have limited impact on beneficiaries' opioid trajectories. However, strong associations between trajectory patterns and beneficiary characteristics provide insight into potential LIP design modifications that might improve program impact. Modifications could include LIP integration of substance use disorder assessment and subsequent referral to treatment, assessment and support for alternate pain therapy services (e.g., physical therapy, biofeedback), and provision of naloxone.

7.2 Introduction

More than half a million people lost their lives to a drug overdose in the United States between 2000 and 2015, as opioid overdose death rates more than tripled.[1] In response to these rapidly escalating rates, numerous policies and programs aimed at reducing opioid addiction and overdose have been implemented.[20] Health insurance sector strategies have included prior authorizations, maximum quantity limits per prescription, formulary controls, letters to high prescribing physicians, and beneficiary "lock-in" programs (LIPs).[19] LIPs are increasingly used across the country by various health plans with the goal of identifying beneficiaries demonstrating potential overutilization of prescription drugs and controlling their access.[33,34] LIPs typically require beneficiaries to use a single prescriber and/or pharmacy to obtain opioids and other specific prescription drugs (e.g., benzodiazepines) for a specified period of time, such as one year.

We previously reported that North Carolina's (NC) Medicaid LIP was associated with reductions in numbers of controlled substance prescriptions, including opioids, dispensed per person per month both while enrolled in the LIP and following release from the program, as compared to a period prior to lock-in.[175] However, dosages of opioids dispensed (in terms of average daily morphine milligram equivalents (MMEs)) to beneficiaries were elevated during LIP enrollment and in the period soon after release from the program.

While understanding the average impact of the program across the LIP-enrolled population is important, this approach can also mask heterogeneous patterns of LIP response. Indeed, prior research indicates that trajectories of substance use vary markedly across populations.[85-89,176] Analyzing variation in opioid dispensing patterns across the LIP-enrolled population can help us better understand *who* responds to LIPs, and in turn help more effectively target limited program resources. In this study, we (1) described heterogeneity in trajectories of dispensed average daily MMEs in a LIP-enrolled beneficiary population, and (2) examined beneficiary characteristics associated with trajectory patterns.

7.3 Methods

We analyzed Medicaid claims linked to Prescription Drug Monitoring Program (PDMP) records for a cohort of beneficiaries enrolled in the NC Medicaid LIP between October 2010 and September 2012 (n= 2,701). Using latent class growth analyses (LCGA)[98], we estimated trajectories of average daily MMEs of opioids dispensed across months prior to, during, and after release from the LIP. We then examined associations between trajectory patterns and demographic characteristics, substance use-related characteristics, comorbid conditions, and overall healthcare utilization.

NC Medicaid LIP

The NC Medicaid LIP originated in October 2010.[173] Medicaid beneficiaries were eligible for the LIP if they met any of the following criteria within two consecutive calendar months: (1) filling more than six opioid prescriptions, (2) filling more than six benzodiazepine prescriptions, or (3) filling opioid or benzodiazepine prescriptions that were written by more than three different prescribers.[173] Each month, LIP-eligible beneficiaries, as determined from Medicaid prescription dispensing information for the previous two months, were prioritized for LIP enrollment using a proprietary algorithm combined with a review process by pharmacists. Based on this prioritization, approximately 200 of the highest ranking beneficiaries were selected for LIP enrollment each month. Beneficiaries were notified of their selection for program enrollment and were informed that LIP enrollment would restrict them for a one-year period to using one prescriber and one pharmacy location to obtain opioid or benzodiazepine prescriptions. Beneficiaries were given 30 days to select a preferred prescriber and pharmacy before restrictions began. Those who did not chose a preferred prescriber and pharmacy were assigned one of each.

Data Sources

As previously described,[175] data included NC Medicaid claims linked to records from the NC Controlled Substances Reporting System (CSRS), NC's PDMP. Linked data were obtained for all beneficiaries enrolled in the LIP between October 2010 and September 2012. In addition to the 12-month LIP period, data were obtained and analyzed for up to 32 months pre-LIP (median of 18 months) and up to 12 months post-LIP release (median of 7 months). NC Medicaid data included beneficiaries' demographic characteristics, periods of Medicaid enrollment, adjudicated pharmacy and medical claims (i.e., inpatient, outpatient, physician, and

108

prescription drug claims), and assigned LIP enrollment and release dates. NC CSRS records

included data on all controlled substances (schedules II-V) dispensed to LIP beneficiaries,

regardless of source of payment (e.g., Medicaid-reimbursed, out-of-pocket). Data were linked

manually using a standardized protocol that included deterministically matching records based

on the first five letters of the beneficiary's last name, date of birth within six months, and the first

two to three letters of the beneficiary's first name.[83]

A small percentage of Medicaid claims for dispensed prescriptions (<7%) were not

captured in the CSRS. Linkage of Medicaid claims to CSRS records allowed for a more

comprehensive enumeration of opioid prescriptions dispensed to beneficiaries. This study was

approved by the University of North Carolina at Chapel Hill's Institutional Review Board.

Study Cohort

We established and followed a historical cohort of adults between the ages of 18 and 64

years who were initially enrolled in the LIP between October 2010 and September 2012 and who

were living independently (e.g., not in a skilled nursing facility) during lock-in. Beneficiaries in

our cohort were followed from the first day that they received an opioid prescription on or after

October 1, 2009 (the first date for which we had data), throughout their period of lock-in, and up

to one year post-program release or until June 30, 2013 (the last date for which we had data),

whichever came first. Because we were particularly interested in understanding different

trajectory paths during and after lock-in, we required cohort beneficiaries to have either remained

continuously enrolled in the LIP (and therefore also Medicaid) for their assigned one-year LIP

period or to have remained continuously enrolled in the LIP through June 2013, the last month

for which we had data (i.e., administrative censoring). We defined continuous enrollment as no

more than a 7-day gap in Medicaid coverage. To balance sample size and generalizability

concerns, there were no requirements regarding continuous Medicaid coverage in the time prior to lock-in or in the year after program release. Those with continuous coverage while enrolled in the LIP had, on average, close to complete Medicaid coverage prior to enrollment as well.[174]

Measures

Outcome Measure

We examined trajectories of average daily MMEs of dispensed opioids across time. Average daily MME is a research measure used to compare diverse opioid medication regimens using morphine equivalents as a standardized unit.[109] To calculate the average daily MME of a given opioid prescription, we multiplied the drug's strength by the quantity received and a medication-specific MME conversion factor and divided by the days' supply received.[114] The average daily MME for each prescription was then applied to all days for which the prescription was to be taken, according to the days' supply. If a beneficiary had more than one opioid prescription active on a given day, the MMEs for all prescriptions to be taken on that day were summed. We included MMEs from all sources of payment (e.g., Medicaid-reimbursed, out-of-pocket). For modeling purposes, we averaged each beneficiary's average daily MMEs across each calendar month. This monthly average measure was then log transformed to obtain an approximately normal distribution for improved model estimation, consistent with previous research.[88]

Covariate Measures

Covariates included demographic characteristics, substance use-related characteristics, comorbid conditions, and overall healthcare utilization.[174,175] Demographic characteristics were assessed at the time of LIP enrollment and included age, gender, race, urbanicity of the beneficiary's county of residence, and Medicaid eligibility category (e.g., qualified based on

disability, as a parent of a dependent child). Substance-use related characteristics, comorbid conditions, and healthcare utilization were assessed using a one-year lookback period from the date of LIP enrollment and included history of alcohol or other substance use-related disorders, history of medication-assisted treatment (MAT) for opioid addiction, history of an overdose event, number of unique pharmacies visited, number of emergency department visits, number of inpatient admissions, history of specific pain-related diagnoses (e.g., arthritis, back, fibromyalgia, sickle cell), history of specific mental health-related diagnoses (e.g., depression, anxiety, bipolar), and Charlson comorbidity index. Specific information on variable categories and claims-related codes used to define characteristics are available in Appendix B. The prevalence of these characteristics in the LIP population have been previously documented (see Chapter 5).[174]

Analysis

Overview of Statistical Models

We used an application of finite mixture modeling, LCGA, to estimate trajectories of average daily MMEs of opioids dispensed to beneficiaries across specific time periods of interest (prior to lock-in, during lock-in, and following release from lock-in). LCGA models identify clusters of individuals that follow approximately the same trajectory for an outcome of interest and can be used as a tool for approximating a complex, unknown distribution of trajectories across the larger population.[96,98,161] LCGA models permit a discrete approximation of the underlying heterogeneity in beneficiary trajectories over time.[96,177]

Model Specification

As a preliminary step, it was necessary to determine how to model the functional form of change in average daily MMEs dispensed over the course of the study period. We considered and

evaluated several model functional forms (e.g., linear, quadratic, cubic, various piecewise specifications), using an unconditional LCGA model. We determined that a five piece, linear piecewise specification provided the best fit. This model aligned with findings from previous analyses involving this cohort.[175] Knots (i.e., points at which slopes were permitted to change) were placed at natural and observed change points, including at the first month of lock-in and at the first month of program release. Additionally, extensive previous analyses revealed a specific spike period with a sharp rise in dispensed opioid prescriptions (and corresponding MMEs), beginning approximately six months prior to lock-in.[175] This spike period appeared to represent the trigger for LIP enrollment for many of these beneficiaries. The spike generally peaked three months prior to enrollment with a decline thereafter. Therefore, knots were also placed at three and six months prior to lock-in (see Figure 7.1).

After having determined the optimal functional form, we conducted a series of analyses to determine how many discrete classes were needed to adequately summarize heterogeneity in growth trajectories. We evaluated one through eight class solutions. All models were fit in Mplus, version 7.4, using robust maximum likelihood estimation (MLR). The five class solution was ultimately selected as the best solution. Full details on criteria used to determine the number of meaningful trajectory classes and the model selection process can be found in Appendix D.

Covariate Associations with Trajectory Classes

LCGA models produce probabilities of belonging to each trajectory class for each beneficiary. Using these posterior probabilities, we estimated the prevalence of beneficiary demographic characteristics, substance use-related characteristics, comorbid conditions, and overall healthcare utilization within each trajectory class. For each trajectory class, we calculated weighted (i.e., weights were posterior probabilities) counts and percentages for categorical

112

covariates and means (with corresponding 25th, 50th, and 75th percentiles) for continuous covariates.

To provide a clearer depiction of covariate relationships with latent classes, we also calculated and graphed standardized differences using the largest class as the reference class. Additional details on these calculations can be found in Appendix E. All analyses of covariate associations with trajectory class were completed in SAS 9.4.

7.4 Results

All five trajectories demonstrated a large spike in average daily MMEs of opioids dispensed during the six months prior to LIP enrollment (Figure 7.1). This escalation period is assumed to be the primary trigger for LIP enrollment. We characterize the five trajectory classes (C) according to their MME levels prior to the spike and following LIP release as follows:

C1) start high (approx. >90 avg. daily MMEs), end high (13.1% of the cohort),

C2) start medium (approx. 20-89 avg. daily MMEs), end medium (13.2%),

C3) start medium, end low (approx.<20 avg. daily MMEs) (21.5%),

C4) start low, end medium (22.6%), and,

C5) start low, end low (29.6%).

More than half (56%) of the LIP-enrolled cohort appeared to cluster around trajectory patterns characterized by a relatively stable level of daily MMEs prior to, during, and following the LIP (i.e., C1, C2, and C5). Prior to becoming eligible (i.e. pre-spike) these three trajectory groups were at high, medium, and low levels of MMEs respectively, and all three were at essentially the same levels post-intervention (i.e., following LIP release).

On the other hand, trajectories C3 and C4 were characterized by considerable change across periods. Compared to their pre-spike period, C4 (23%) had an unexpected increase in MME dosage during lock-in and following release. Of the five groups, only C3 (22%) exhibited a decline in dispensed MMEs during the lock-in period. However, this decline was evident prior to the point of actual LIP enrollment (Figure 7.1) and, therefore, a causal association remains questionable.

Covariate Associations with Trajectories

Covariate similarities and differences were summarized (Tables 7.1, 7.2; Figure 7.2). Comparisons of particular interest are presented below.

C1 and C2 (sustained high or medium MMEs) compared to C5 (sustained low MMEs): Approximately one quarter of our cohort tended to obtain average daily MMEs in high or medium dosage amounts across all time periods (i.e., C1 and C2). Despite their different MME levels, beneficiaries that clustered around these two trajectories tended to be similar in terms of their covariate profiles. They were older, on average, than other trajectory classes, and tended to have higher levels of chronic pain, disability, and comorbidity. At the other extreme, beneficiaries following C5, a trajectory characterized by sustained low levels of MME dispensing across time, were the youngest of all classes, had the lowest levels of chronic pain, comorbidity, and disability, and had the highest levels of addiction treatment.

C2 and C3 (both began at medium MMEs, C3 declined while C2 remained level): C2 and C3 were relatively similar in pre-spike levels of dispensed MMEs but differed considerably with respect to post-spike trajectories. C3 exhibited a large decline in MMEs following the spike in opioid dispensing, in contrast to C2's sustained levels. While beneficiaries who tended to follow these patterns were generally similar in terms of average covariate characteristics, beneficiaries

clustered around a C3 trajectory had the highest prevalence of overdose events and substance-related disorder diagnoses prior to LIP enrollment, as well as a relatively high prevalence of MAT and mental health disorder diagnoses.

C4 and C5 (both began at low MMEs, C4 elevated while C5 remained low): C4 and C5 were similar in pre-spike levels of dispensed MMEs. However, C5 returned to a low level of MME dispensing following the spike, while C4 remained at a heightened level following the spike. Most striking was the difference in MAT use associated with these two trajectories: C5 had the highest use of MAT, nearly four times that of C4. Other notable differences included a higher prevalence of beneficiaries receiving Medicaid benefits due to a disability, a higher prevalence of severe pain diagnoses, and a higher mean comorbidity index among beneficiaries following a C4 trajectory.

7.5 Discussion

Among a beneficiary population receiving large numbers of opioid prescriptions, considerable heterogeneity existed in the trajectories of opioid dosages (MMEs) dispensed prior to, during, and following release from a Medicaid LIP. We found that five trajectory patterns provided a suitable summary of the underlying heterogeneity in MME trajectories and that there were notable associations between trajectory patterns and beneficiaries' demographic characteristics, substance use-related characteristics, comorbid conditions, and overall healthcare utilization.

Covariate Associations with Trajectories

While previous research has demonstrated considerable heterogeneity in classes of controlled substance users,[85-89,176] this is the first study to examine opioid dispensing trajectories

within a specific population of beneficiaries exhibiting high opioid utilization who were included in an intervention aimed at reducing potential overutilization. Therefore, there is little research to which to compare our findings. From a broad perspective, studies have identified similar covariates, including mental health disorders, severity of pain conditions, and healthcare utilization, associated with dissimilar classes of controlled substance users.[86,90]

Key covariate differences between C2 and C3 suggest that declines in C3 opioid dispensing post-spike could be attributed to the higher prevalence of overdose events and MAT in this class. Specifically, overdose events could have served as an impetus for MAT and the observed decline in MMEs prior to and during enrollment for some beneficiaries clustering around C3. However, additional research is needed to more closely examine the temporality of these associations and to also examine the extent to which mental health disorders and associated treatment may or may not have contributed to the declining pattern. Given that the decline began prior to enrollment in the LIP, beneficiaries clustered around the C3 pattern might have followed a declining pattern post-spike, irrespective of LIP enrollment. Additional work is needed to understand whether the LIP had any impact on the decline in C3.

Compared with beneficiaries in C5, those following a C4 pattern tended to have a greater prevalence of pain conditions, disability, and comorbidity. If these beneficiaries experienced an onset of new pain conditions, disabilities, and/or comorbidities just prior to meeting LIP eligibility, this might help explain why they escalated and remained elevated at the time that they did, rather than returning to MME dispensing levels similar to pre-spike levels, like C5. Additionally, while it seems likely that the large proportion of MAT may have factored into the re-stabilization to low levels of dispensed MMEs observed in the C5 trajectory, the majority of beneficiaries clustered around this class did not use MAT. Additional work is needed to

understand factors driving the observed spike in opioid dispensing in this population, and reasons why certain beneficiaries re-stabilize post-spike while others do not.

LIP Implications

LIPs are generally implemented to reduce potential overutilization of opioids among beneficiaries; however, our findings suggest limited impact on average trajectories of MMEs dispensed to beneficiaries over LIP-related periods. The only class that exhibited a decline in dispensed MMEs during the lock-in period was C3; however, this decline was evident prior to the point of actual LIP enrollment. These findings cast doubt on the ability of the LIP to influence beneficiary trajectories.

Our findings, combined with early evidence from promising LIP designs,[68] suggest that there may be modifications LIPs can make to operate more effectively and improve beneficiary outcomes. For example, given our finding of a strong association of MAT history with generally low MME trajectory patterns, LIP administrators could consider comprehensively integrating a range of substance use disorder assessment and treatment services throughout LIP pre-enrollment and enrollment periods. Additionally, we found that those receiving Medicaid benefits due to a disability tended to follow paths characterized by higher levels of dispensed MMEs across periods. A focused effort, as part of the LIP, to assess beneficiaries who receive Medicaid benefits due to a disability and remain at persistently high levels of MMEs for potential opioid tapering, utilization of alternative or complementary pain therapy approaches, and possession of naloxone might improve beneficiary outcomes and reduce overdose risk.[178]

Limitations

Our findings should be viewed in light of four limitations. First, we used LCGA as an exploratory tool to begin to examine potential underlying heterogeneity in the trajectories of

117

dispensed opioid dosages obtained by beneficiaries across LIP-related periods. Research

suggests that these methods can be vulnerable to model misspecification, and while we used

several model selection and diagnostic criteria, further analyses in similar LIP populations

should be conducted to examine the consistency of findings.[179,180] Second, while the linked

Medicaid claims-CSRS database likely captured nearly all opioids dispensed to these patients,

there are some gaps in understanding patients' complete opioid acquisition. We do not have

information on opioid prescriptions acquired across state lines, from pharmacies located on

military bases or veterans' administration hospitals, or obtained through illicit sources. Third, the

extent to which pain-related diagnoses represented actual pain-related conditions is unknown. To

the extent that some beneficiaries were drug seeking and did not have a painful condition, the

prevalence of these conditions may be overestimated. However, poor coding of the conditions on

claims could also lead to underestimation. Fourth, the presence of diagnoses in the year prior to

LIP enrollment may be underestimated. However, research suggests that inclusion of any

available data in a lookback period to assess presence of covariates results in less

misclassification than restricting the data to a common lookback period for all persons.[169]

Conclusions

Understanding heterogeneous patterns in amounts of dispensed opioids and

corresponding associations with beneficiary characteristics can provide insight into the design

and implementation of LIPs. Our findings suggest that greater assessment of substance use

disorders and subsequent referral to MAT may lead some beneficiaries to follow lower risk

opioid dispensing trajectories. Additionally, administrators might consider assessing

beneficiaries found to follow persistently high MME trajectories, including those with

disabilities, severe pain diagnoses, and high levels of comorbidity, for uptake of alternate pain

therapy services (e.g., physical therapy, biofeedback) and other overdose risk reduction strategies (e.g., access to naloxone). Finally, additional research to understand factors that drive spikes in opioid dispensing and to identify other intervention components that could beneficially alter opioid trajectories may help improve LIP designs and ultimately beneficiaries' outcomes.

Figure 7.1 Trajectories^ of log of average daily morphine milligram equivalents (MME) of opioids dispensed to beneficiaries enrolled in the North Carolina Medicaid "lock-in" program per month, October 2009-June 2013 (n=2,701)
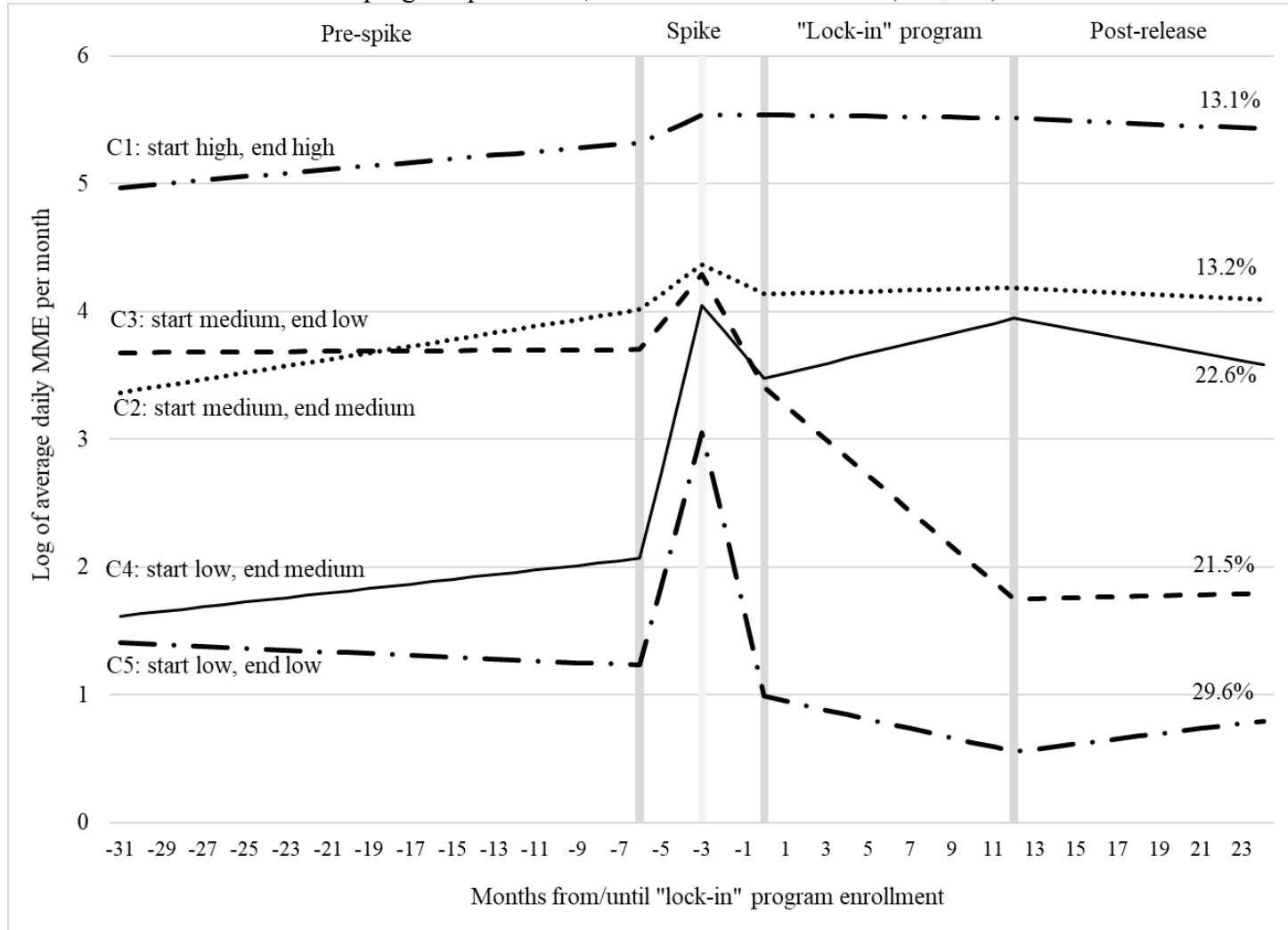
^ Estimated means from five class, five-piece linear piecewise latent class growth analysis model
C=Class. Percentages are latent class proportions based on posterior probabilities. Grey vertical lines indicate where knots were placed in the piecewise model.
Pre-spike period= more than 6 months prior to "lock-in" program enrollment; Spike period= 0-6 months prior to "lock-in" program enrollment; "Lock-in" program period= 12-month enrollment period; Post-release period= 12 months after disenrollment from the "lock-in" program

Table 7.1 Weighted* counts, percentages, and means for characteristics of each of the five latent classes representing different trajectories in the log of average daily morphine milligram equivalents (MME) of opioids dispensed to beneficiaries enrolled in the North Carolina Medicaid "lock-in" program per month, October 2009-June 2013

	Total Cohort (n=2,701)	Start high, end high (C1) (n=353.0; 13.1%)*	Start medium, end medium (C2) (n=357.6; 13.2%)*	Start medium, end low (C3) (n=581.3; 21.5%)*	Start low, end medium (C4) (n=609.4; 22.6%)*	Start low, end low (C5) (n=799.8; 29.6%)*
		N (%) for categorical variables; Mean (25th pct, median, 75th pct) for continuous variables				
DEMOGRAPHICS^						
Age (years)	38.7 (30, 38, 47)	43.6 (37, 44, 52)	43.6 (36, 44, 51)	39.5 (31, 39, 47)	38.6 (31, 38, 46)	33.9 (27, 32, 40)
Gender						
Women	1,896 (70.2)	216.2 (61.3)	233.3 (65.3)	386.9 (66.6)	446.3 (73.2)	613.3 (76.7)
Men	805 (29.8)	136.8 (38.8)	124.2 (34.7)	194.4 (33.4)	163.1 (26.8)	186.5 (23.3)
Race						
White	1,999 (74.0)	268.0 (75.9)	246.4 (68.9)	424.8 (73.1)	433.4 (71.1)	626.4 (78.3)
Black	550 (20.4)	66.9 (19.0)	86.3 (24.1)	116.6 (20.1)	133.6 (21.9)	146.5 (18.3)
Other	152 (5.6)	18.0 (5.1)	24.9 (7.0)	39.9 (6.9)	42.3 (7.0)	26.9 (3.4)
Urbanicity of county of residence						
Counties in metro areas of ≥ 1 mill. pop.	675 (25.0)	65.9 (18.7)	86.1 (24.1)	137.5 (23.7)	161.4 (26.5)	224.1 (28.0)
Counties in metro areas of < 1 mill. pop.	1,268 (47.0)	180.8 (51.3)	162.3 (45.4)	269.7 (46.4)	276.9 (45.4)	378.3 (47.3)
Nonmetro, urban pop. of ≥ 20,000	444 (16.4)	54.2 (15.4)	73.3 (20.5)	102.8 (17.7)	111.7 (18.3)	102.0 (12.8)

Nonmetro, urban pop. of <20,000 or rural pop.	314 (11.6)	51.9 (14.7)	35.9 (10.1)	71.4 (12.3)	59.3 (9.7)	95.4 (11.9)
Medicaid eligibility category						
Aid to families with dependent children	1,389 (51.4)	119.4 (33.8)	135.5 (37.9)	267.0 (45.9)	347.9 (57.1)	519.2 (64.9)
Aid to disabled	1,282 (47.5)	232.5 (65.9)	219.0 (61.3)	311.2 (53.5)	259.6 (42.6)	259.7 (32.5)
Aid for other reasons (e.g., aid to blind)	30 (1.1)	1 (0.3)	3.0 (0.8)	3.2 (0.6)	1.9 (0.3)	20.9 (2.6)
SUBSTANCE USE-RELATED †						
Alcohol-related disorder	174 (6.4)	18.5 (5.3)	30.8 (8.6)	38.4 (6.6)	35.0 (5.7)	51.2 (6.4)
Other substance-related disorder	870 (32.2)	110.3 (31.2)	82.7 (23.1)	214.7 (36.9)	171.9 (28.2)	290.4 (36.3)
Medication-assisted treatment (MAT)	273 (10.1)	7.5 (2.1)	4.1 (1.1)	43.8 (7.5)	37.7 (6.2)	180.0 (22.5)
Medication or drug-related overdose	193 (7.2)	29.8 (8.4)	23.1 (6.5)	58.2 (10.0)	33.0 (5.4)	49.0 (6.1)
HEALTH CARE UTILIZATION †						
Number of unique pharmacies from which Medicaid-reimbursed prescriptions were obtained	4.2 (2, 4, 6)	3.7 (2, 3, 5)	4.0 (2, 4, 5)	4.4 (3, 4, 6)	4.3 (3, 4, 6)	4.2 (3, 4, 5)

Emergency department visits	9.9 (3, 6, 13)	5.5 (1, 3, 7)	9.4 (2, 5, 12)	10.8 (3, 7, 14)	10.3 (3, 7, 13)	11.3 (4, 8, 14)
Inpatient admissions	1.3 (0, 1, 2)	1.6 (0, 1, 2)	1.5 (0, 1, 2)	1.6 (0, 1, 2)	1.2 (0, 1, 2)	1.0 (0, 1, 1)
PAIN-RELATED DIAGNOSES †						
Any joint pain or arthritis	2,452 (90.8)	325.4 (92.2)	338.9 (94.8)	549.3 (94.5)	571.7 (93.8)	666.7 (83.4)
Back pain	2,253 (83.4)	308.4 (87.4)	309.0 (86.4)	504.3 (86.8)	535.0 (87.8)	596.3 (74.6)
Neck pain	1,124 (41.6)	141.4 (40.1)	165.4 (46.3)	252.9 (43.5)	277.3 (45.5)	287.1 (35.9)
Headache/migraine pain	589 (21.8)	63.3 (17.9)	80.1 (22.4)	131.6 (22.6)	146.5 (24.0)	167.5 (21.0)
Fibromyalgia, chronic pain, or fatigue	1,443 (53.4)	261.1 (74.0)	230.8 (64.5)	363.1 (62.5)	353.5 (58.0)	234.6 (29.3)
Rheumatoid arthritis or osteoarthritis	706 (26.1)	144.5 (41.0)	139.0 (38.9)	168.0 (28.9)	160.0 (26.3)	94.4 (11.8)
Sickle cell	50 (1.9)	17.3 (4.9)	9.8 (2.7)	11.7 (2.0)	10.0 (1.6)	1.2 (0.2)
MENTAL HEALTH-RELATED DIAGNOSES †						
Depression	1,675 (62.0)	193.6 (54.9)	221.6 (62.0)	364.0 (62.6)	388.0 (63.7)	508.8 (63.5)
Anxiety disorder	1,184 (43.8)	123.2 (34.9)	136.6 (38.2)	288.6 (49.6)	275.7 (45.2)	360.0 (45.0)
Other serious mental health disorder (e.g., bipolar, schizophrenia)	751 (27.8)	59.5 (16.9)	71.6 (20.0)	189.1 (32.5)	172.9 (28.4)	257.9 (32.3)
COMORBID CONDITION INDEX †						
Mean Charlson comorbidity index	0.92 (0, 0, 1)	1.31 (0, 1, 2)	1.20 (0, 1, 2)	0.98 (0, 0, 1)	0.93 (0, 0, 1)	0.57 (0, 0, 1)

pct= percentile; C= class

* Weights are estimated posterior probabilities for belonging to a given class

^ Assessed at the time of "lock-in" program enrollment

† Assessed using a one-year lookback period from the date of "lock-in" program enrollment

Figure 7.2 Standardized differences* in North Carolina Medicaid "lock-in" program-enrolled beneficiary characteristics by latent class, using class 5 (i.e., "low MME other than spike period" class) as the reference group
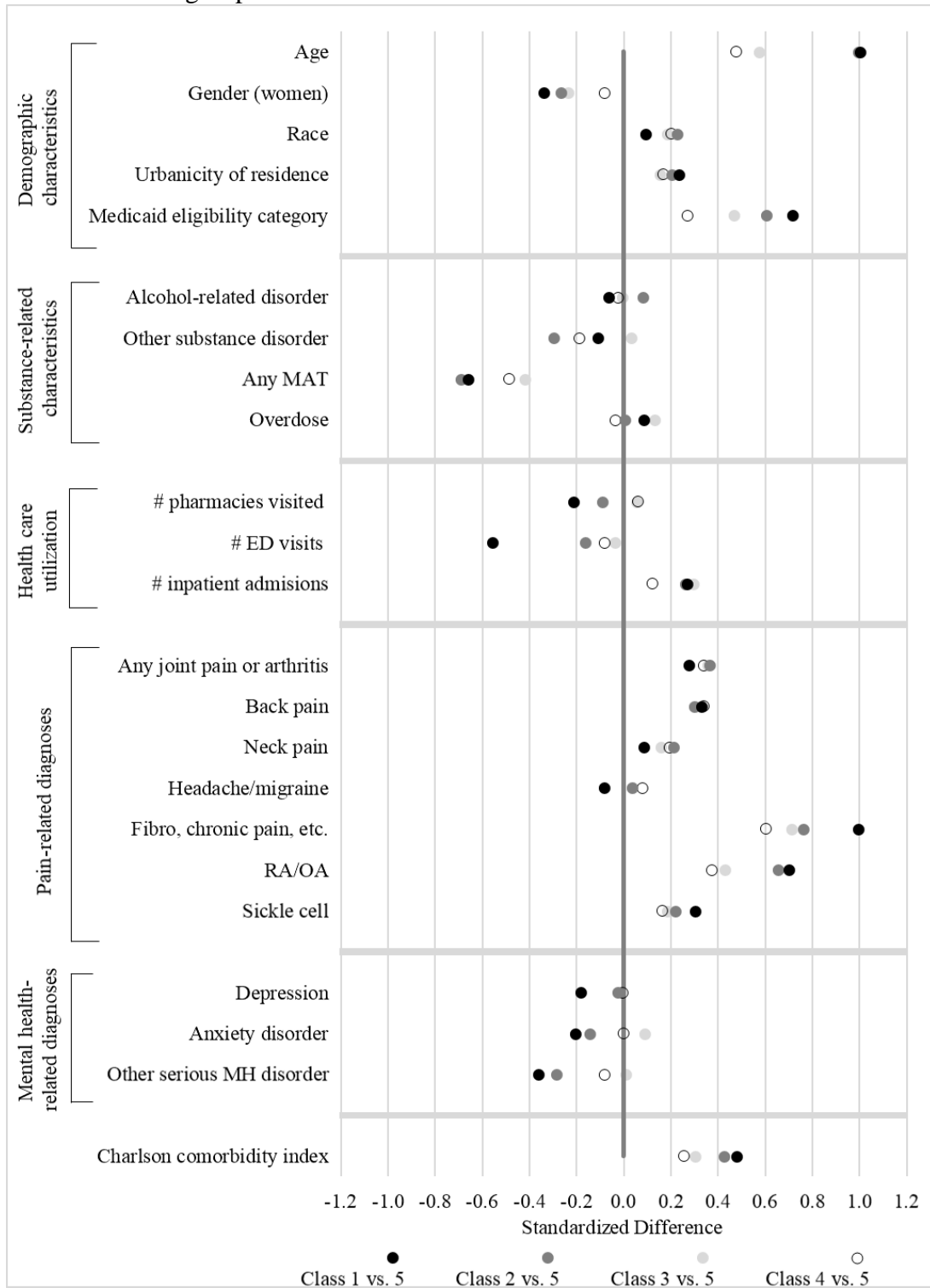
MAT= medication-assisted treatment; ED= emergency department; RA/OA= rheumatoid arthritis/osteoarthritis; MH= mental health; Class 1= start high, end high; Class 2= start medium, end medium; Class 3= start medium, end low; Class 4= start low, end medium; Class 5= start low, end low

* Refer to Appendix E for details on standardized difference calculations. Briefly, standardized differences provide a measure of the similarity or dissimilarity of two groups with respect to specific covariates. For example, for "other substance disorders," the figure indicates that beneficiaries who cluster around Classes 1, 2, and 4 have a lower prevalence of substance disorders than those who cluster around Class 5, and beneficiaries who cluster around Class 3 have a somewhat higher prevalence of substance disorders than those who cluster around Class 5.

Table 7.2 Key characteristics of beneficiaries enrolled in the North Carolina Medicaid "lock-in" program by latent class (n=2,701)

Latent class number/description	Summary of key characteristics associated with trajectory pattern
C1: Start high, end high	Older than C3-5; highest proportion of men; highest prevalence receiving Medicaid due to a disability; lower prevalence of MAT compared to C3-5; lowest mean ED visits; highest prevalence of severe pain diagnoses; lowest prevalence of mental health disorders; highest mean comorbidity index
C2: Start medium, end medium	Similar to C1 in many characteristics (e.g., age, gender, Medicaid eligibility category, pain diagnoses); different than C1 in greater use of ED; slightly lower prevalence of other substance-related disorder diagnoses
C3: Start medium, end low	Younger than C1&2; less disability than C1&2; greater use of MAT than C1&2; highest prevalence of other substance use-related disorders and overdose; greater use of ED than C1&2 and similar to C4&5; higher prevalence of mental health disorders than C1&2 and similar to C4&5
C4: Start low, end medium	Similar in age to C3, older than C5; larger proportion of women than C1-3, similar to C5; lower prevalence of disability than C1-3, more than C5; similar use of MAT to C3 but lower than C5; similar prevalence of pain diagnoses to C3, higher than C5; similar prevalence of mental health diagnoses to C3&5; higher mean comorbidity index than C5, similar to C3
C5: Start low, end low	Younger than C1-C4; highest prevalence of women; lowest prevalence of disability; very high prevalence of MAT (highest of any class); highest use of EDs; lowest prevalence of severe pain diagnoses; high prevalence of mental health disorders, similar to C3&4 and higher than C1&2; lowest comorbidity index

C= class (trajectory); MAT= medication-assisted treatment; ED= emergency department

CHAPTER 8—DISCUSSION

8.1 Overall Findings

In this dissertation, we had two primary aims: 1) to assess the impact of exposure to the NC MLIP on numbers of dispensed CS prescriptions and the dosages of opioids dispensed in the year following release from the MLIP (see Chapter 6) and 2) to examine heterogeneity in beneficiaries' trajectories of dispensed opioid dosages across periods prior to, during, and following release from the MLIP (see Chapter 7).

To inform both Aim 1 and Aim 2 analyses, including the construction of the analytic cohort for these aims, we first conducted a detailed analysis of the beneficiaries eligible for, enrolled in, and retained in the MLIP (see Chapter 5). We found that compared to beneficiaries who were eligible for but not enrolled in the MLIP, enrolled beneficiaries were more likely to 1) have substance use and mental health disorders, 2) obtain controlled substances from multiple pharmacies, and 3) visit emergency departments. They were also less likely to receive Medicaid benefits due to a disability or to be diagnosed with cancer or other severe comorbid conditions. We also found that compared to those who completed the 12-month MLIP, those who exited the MLIP early (due to loss of Medicaid benefits) were younger and more likely to 1) obtain controlled substances from multiple pharmacies, 2) reside in counties with high opioid overdose death rates, and 3) have less stable Medicaid coverage prior to MLIP enrollment.

To accomplish Aim 1 (see Chapter 6), we then constructed a cohort of beneficiaries enrolled in the MLIP for a full 12 months (or enrolled continuously until administrative censoring). Based on findings described above, we restricted the analytic cohort in this way to avoid conflating program effects for those who remained continuously enrolled in the MLIP and those who exited the MLIP prior to completion. Using GEE to estimate program effects on dispensed CS, we found that prescriptions for opioids and other CS spiked in the 6 months prior to MLIP enrollment, which was a trigger for MLIP enrollment. Compared to the pre-spike period (>6 months prior to MLIP enrollment), numbers of dispensed CS per month during and following release from the MLIP were slightly lower (count difference (CD) per person-month: -0.05; 95% CI: -0.11, 0.01 and CD: -0.23; 95% CI: -0.31, -0.15, respectively). Stratification by payer source revealed that decreases in Medicaid-reimbursed prescriptions during enrollment and following release were offset considerably by increases in non-Medicaid-reimbursed prescriptions (e.g., out-of-pocket payments) during these periods. Notably, we also found that beneficiaries' average daily MMEs of dispensed opioids were elevated both during and following release from the MLIP, compared to the pre-spike period (mean difference (MD): 18.7; 95% CI: 13.9, 23.6 and MD: 11.1; 95% CI: 5.1, 17.1, respectively). Stratification by payer source also revealed increases in average daily MMEs obtained from non-Medicaid-reimbursed prescriptions during MLIP enrollment with a persistent impact following release.

Finally, in Aim 2 (see Chapter 7), we examined heterogeneity in beneficiaries' trajectories of average daily MMEs of dispensed opioids across periods prior to, during, and following release from the MLIP. Using LCGA models, we found that five trajectory patterns appeared to appropriately describe the underlying heterogeneity in average daily MME trajectories. All patterns demonstrated a spike in MMEs of dispensed opioids in the six months

prior to lock-in, which clearly constituted a trigger for MLIP enrollment. However, the patterns were dissimilar both in regards to overall starting values (intercepts) and slopes. We described the five patterns as: 1) high, sustained MMEs across all MLIP-related periods (13.1% of the cohort); 2) moderately high, stable MMEs across all MLIP-related periods (13.2%); 3) large decline in MMEs following spike (21.5%); 4) low MMEs prior to spike with sustained, moderately high MMEs following spike (22.6%); and 5) low MMEs across all periods, other than spike (29.6%). We also found that several covariates were associated with the probability of following specific trajectory patterns. For example, compared to the trajectory with low MMEs across all periods, the trajectory of high, sustained MMEs was associated with older age, male sex, greater likelihood of receiving Medicaid benefits due to a disability, low use of MAT for opioid addiction in the year prior to lock-in, fewer ED visits but more inpatient admissions in the year prior to lock-in, increased prevalence of severe pain diagnoses (e.g., chronic pain, rheumatoid arthritis/osteoarthritis, sickle cell), higher mean comorbidity index, and lower prevalence of mental health disorders.

8.2 Limitations

While we have described the specific limitations of each analysis conducted as part of this dissertation in the "Discussion" subsections of Chapters 5-7, we briefly summarize some of the overall limitations below.

First, due to the intensive work required to link Medicaid claims and CSRS records, only beneficiaries enrolled in the MLIP at some point between October 2010 and September 2012 had their data linked and were captured in the analytic data set. In other words, we did not have linked data on persons who were never "exposed" to the MLIP. While this group would have

been useful as a control, we compensated in Aim 1 analyses by incorporating a novel method to control for changes in secular trend over time using Medicaid claims data from those eligible but not enrolled in the MLIP. Moreover, our repeated measures analyses in which everyone contributed data for a period prior to MLIP enrollment allows for persons to serve as their own control in a sense. This combination of design and analytic control measures was expected to reduce bias in our longitudinal analyses, similar to the use of a traditional control group. In Aim 2 analyses, complete data on all MMEs acquired by those never "exposed" to the MLIP would have been also useful. However, in Section 8.5 ("Future Research Directions"), we discuss how Medicaid claims from the MLIP-eligible but never enrolled cohort was again used in sensitivity analyses to further explore Aim 2 trajectory findings.

Second, while the CSRS database captures almost all CS dispensed to beneficiaries, there were still some gaps in understanding beneficiaries' complete CS use. We do not have information on CS prescriptions acquired across state lines or those obtained through illicit sources. Moreover, we found that a small percentage (<7%) of CS claims in Medicaid did not have a matching record in the CSRS. However, previous analyses revealed no obvious signs of systematic missingness with respect to these records.[79] Lastly, as with any pharmacy claims-based analyses, we cannot assume that all dispensed CS were actually consumed by the beneficiary.

Third, as in most studies, there is the chance of residual confounding resulting from incomplete control of variables on biasing "paths" between MLIP exposure and our CS-related outcomes. While we examined the impact of adjusting for several potential confounders on our measures of association in our Aim 1 analyses, adjustments had to be carried out one at a time,

due to modeling constraints. In other words, we were unable to examine the impact of including a minimally sufficient set of potential confounders in a model all at the same time.

Finally, LCGA and other growth curve modeling methods are novel methods that (like other advanced methods) can be vulnerable to model misspecification.[179,180] However, we included several model selection and diagnostic criteria to help us achieve our goal of understanding the underlying heterogeneity in trajectories of beneficiaries' opioid dosages over time. Still, further analyses in similar MLIP populations should be conducted to examine the consistency of findings.

8.3 Strengths

This dissertation makes a unique and important contribution to the prescription opioid-related policy literature. We utilized a unique, linked data set to answer critical questions about the impacts of a MLIP. This large, multi-year data set allowed us to examine sustained effects of NC's MLIP, filling a key gap in the literature with respect to understanding larger program impacts. This dissertation was also innovative in its application of advanced methods to the question of whether the trajectories of dispensed opioid dosages changed across periods prior to MLIP enrollment, during lock-in, and following lock-in release for different strata of the beneficiary population. This study is the first to explore such heterogeneity across MLIP-related periods. The findings from this dissertation, combined with key results from previous analyses of this data, provide a foundation that will inform recommendations for future MLIP policy improvements.

131

8.4 Policy Implications

Overall, the NC MLIP appears to generally identify a high-risk subpopulation of beneficiaries with many comorbidities (e.g., substance use, mental health, pain). However, the program, in its current form, was associated with unintended consequences, not only while enrolled but also following release. We found that the MLIP was associated with acquiring a greater proportion of CS prescriptions using non-Medicaid payment sources both during MLIP enrollment and following release, as compared to a pre-MLIP enrollment period. Moreover, beneficiaries acquired greater dosages of dispensed opioids, in terms of average daily MMEs, from both Medicaid and non-Medicaid payment sources.

These findings further suggest that the MLIP may result in reduced opioid dosages for few beneficiaries. We found that nearly 80% of the MLIP-enrolled cohort tended to cluster around trajectory patterns characterized by relatively stable or increasing MME dosages during lock-in and following release, as compared to prior to enrollment (and prior to the unstable spike period that triggered enrollment). Moreover, the only trajectory pattern characterized by a decline in dispensed MMEs during the lock-in period exhibited this decline prior to the point of actual MLIP enrollment. Therefore, our findings cast doubt on the ability of the MLIP to influence beneficiary trajectories of dispensed MMEs.

Taken together, the results chapters of this dissertation suggest that MLIP-enrolled beneficiaries may benefit from provision and coordination of additional services (e.g., screening and connection to substance abuse, mental health, and alternative pain therapy services) offered as part of the MLIP. Such services might help address important unintended consequences and increase the overall utility of these programs. Refining MLIPs to increase provider utilization of PDMP data may help improve coordination of care and reduce unintended program impacts

(e.g., increases in using non-Medicaid payment). Recent Substance Abuse and Mental Health Services Administration-funded projects, entitled PDMP Electronic Health Records Integration and Interoperability Expansion projects, in nine states suggest that increased integrated of PDMP data into health information exchanges, electronic health record systems, and/or pharmacy dispensing software systems can streamline provider access and increase provider PDMP use.[181] NC could consider examining the growing evidence base from projects, such as these, to inform improved PDMP integration with Medicaid and other systems throughout the state.

Finally, given that all programs have finite resources, our findings of heterogeneous patterns in dosages of dispensed opioids and associations with beneficiary characteristics provide insight into how MLIP administrators could begin to further focus program resources. Our findings suggest that greater assessment of substance use disorders and subsequent referral to MAT may lead some beneficiaries to follow lower risk opioid dispensing trajectories. Additionally, administrators might consider assessing beneficiaries found to follow persistently high MME trajectories, including those with disabilities, severe pain diagnoses, and high levels of comorbidity, for uptake of alternate pain therapy services (e.g., physical therapy, biofeedback) and other overdose risk reduction strategies (e.g., access to naloxone).

8.5 Public Health Impact

In this dissertation, we conducted the first studies to examine the sustained impacts of a MLIP and to gain a detailed understanding of heterogeneity in pre-, during, and post-MLIP opioid dispensing patterns. By making use of a unique linked database and innovative methods, findings from this dissertation can be used to guide health policy to help address prescription opioid misuse, addiction, and overdose.

Even small changes in the dosages of opioid prescriptions filled can translate to larger impacts beyond Medicaid. Research shows that among all those prescribed opioids, approximately 80% are prescribed low doses (<100 MMEs per day) by a single prescriber, and they experience about 20% of opioid-related overdoses.[138,182] An additional 10% of are prescribed high does (≥100 MMEs per day) by a single prescriber and experience about 40% of overdoses.[111,112] The remaining 10% obtain opioids from multiple prescribers and have high daily doses.[122] These patients represent a notable proportion of the types of patients who are enrolled in programs like MLIPs. Research shows they are not only at high risk of overdose themselves but may also be involved in the diversion of opioids to others.[122] In fact, studies from West Virginia, Ohio, and Utah have found that 25%-66% of those who died of a prescription opioid overdose used opioids that were originally prescribed to someone else, and national estimates have shown that nearly 70% of nonmedical opioid users report getting their opioids from a friend or relative, rather than a doctor.[118,122,183,184] Based on these studies and others, agencies like the CDC have recommended that overdose prevention efforts focus on those using high doses and seeking opioids from multiple prescribers in order to reduce the supply diverted to the larger community.[185] Therefore, while this dissertation focused on a specific and relatively small population, it is important to note that program impacts also likely have ancillary effects on the overall opioid use, misuse, and overdose in NC communities.

8.6 Future Research Directions

Findings from this dissertation indicate several areas for future research. We highlight four key areas below.

First, research on identification of optimal MLIP eligibility criteria is needed. While we found that overall MLIP enrollment processes appeared to identify a high-risk beneficiary population who might benefit for improved coordination of services, we also found specific trajectory patterns characterized by beneficiaries who were routinely dispensed low dosages of opioids (other than a confined spike in dispensing). It may be that MLIP resources are not effectively used by enrolling those who cluster around trajectories of routinely low opioid dispensing, and research is needed to examine how best to identify beneficiaries with the potential to benefit the most from a MLIP.

Second, further research is needed to understand contributing factors to spikes in opioid and CS dispensing. We found that spikes in numbers and dosages of CS dispensed, in the months just prior to MLIP enrollment, were not unique to MLIP-enrolled population, but also occurred in Medicaid beneficiaries who met the MLIP eligibility criteria but were not enrolled (see Appendix A). These spike periods revealed important information regarding the average CS utilization trajectory leading to eligibility for the MLIP; however, they also led us to call into question the suitability of current MLIP eligibility and enrollment processes and the overall impacts of the MLIP. Understanding whether some beneficiaries experience an isolated spike in dispensing due to relocation, legitimate changes in providers, or a brief episode in breakthrough pain that largely resolves itself, as opposed to repeated spikes in opioid dispensing behaviors indicative of potential diversion or illegitimate use, could help further focus enrollment criteria and program design.

Third, while this dissertation provided important insights on sustained and differential impacts of the MLIP on CS prescriptions and opioid dosages dispensed, additional work is needed to also examine MLIP impacts on beneficiary health outcomes, such as overdose, and use

of other key health services, such as substance use disorder treatment (e.g., MAT).[186] Given our findings of increased dispensed MMEs, on average, during and following release from lock-in and previous research suggesting a dose-dependent relationship between average daily MMEs and opioid overdose risk [110-112], future studies are needed to explore potential changes in overdose risk across MLIP-related periods. Additionally, given our finding that nearly a quarter of MLIP enrollees had a diagnosis of a substance use-related disorder in the year prior to enrollment, research on the availability and use of substance use disorder treatment, such as medication-assisted therapy, prior to, during, and following MLIP release is warranted.

Finally, additional work is needed to understand specific MLIP impacts on heterogeneous opioid dispensing and health outcome trajectories. Our finding that average opioid dosage trajectories were generally characterized by relatively stable or increasing MME patterns during lock-in and following release, as compared to prior to MLIP enrollment, indicated that the program may have had little influence on opioid trajectories. To examine this further, we conducted sensitivity analyses in a MLIP-eligible, but never enrolled, population of Medicaid beneficiaries (Appendix F). These analyses revealed similar trajectory patterns to the MLIP-enrolled, and similar covariate associations with patterns, also suggesting little influence of the program on overall trajectories and potentially greater influence from covariate profiles. Sensitivity analyses were limited in that 1) we did not have CSRS records on those who were never enrolled in the MLIP, only Medicaid claims and 2) the time axis inevitably differed from our primary analysis. In our primary analysis, the MLIP-enrolled cohort was examined from time until/from MLIP enrollment; however, the never enrolled cohort could only be examined using time until/from first meeting MLIP eligibility criteria. Therefore, while initial findings suggest little program influence on heterogeneous trajectories, studies designed to specifically analyze

MLIP impacts on trajectories of not only opioid dispensing but also health outcomes (e.g., overdose) are needed.

8.7 Summary

In this dissertation, we 1) examined the sustained impact of the NC MLIP on dispensed CS and dosages of opioids dispensed (in terms of MMEs) and 2) examined whether trajectories of MMEs differed across time prior to, during, and following release from the MLIP for different strata of the population. Data included NC Medicaid claims linked to records from NC's PDMP from October 2009 through June 2013.

We found that compared to a period of stable CS dispensing prior to MLIP enrollment, the MLIP reduced the average numbers of CS dispensed both during lock-in and following release. However, the program was also associated with increased acquisition of dispensed CS using non-Medicaid payment (e.g., out-of-pocket) both during lock-in and following release. Moreover, beneficiaries acquired greater MMEs of dispensed opioids from both Medicaid and non-Medicaid payment sources during lock-in and following release.

We also found that considerable heterogeneity existed in trajectories of MMEs of dispensed opioids across time prior to, during, and following release from the MLIP. Five trajectory patterns appeared to sufficiently describe underlying heterogeneity. All patterns demonstrated a spike in MMEs in the six months prior to lock-in, constituting a trigger for MLIP enrollment; however, patterns were dissimilar in overall starting values and slopes. While the trajectories indicated that the MLIP may have had little influence on MME patterns across time, strong associations between trajectory patterns and beneficiary characteristics were evident.

Findings from this dissertation will help inform the development of future MLIP improvements both in NC and across the US.

APPENDIX A—AVERAGE DAILY MORPHINE MILIGRAM EQUIVALENTS (MMEs) AMONG BENEFICIARIES ENROLLED IN THE NORTH CAROLINA MEDICAID "LOCK-IN" PROGRAM (MLIP), BY SOURCE OF PAYMENT, AND AMONG ELIGIBLE BUT NEVER MLIP-ENROLLED BENEFICIARIES BY TIME UNTIL/FROM FIRST MEETING MLIP-ELIGIBILITY CRITERIA
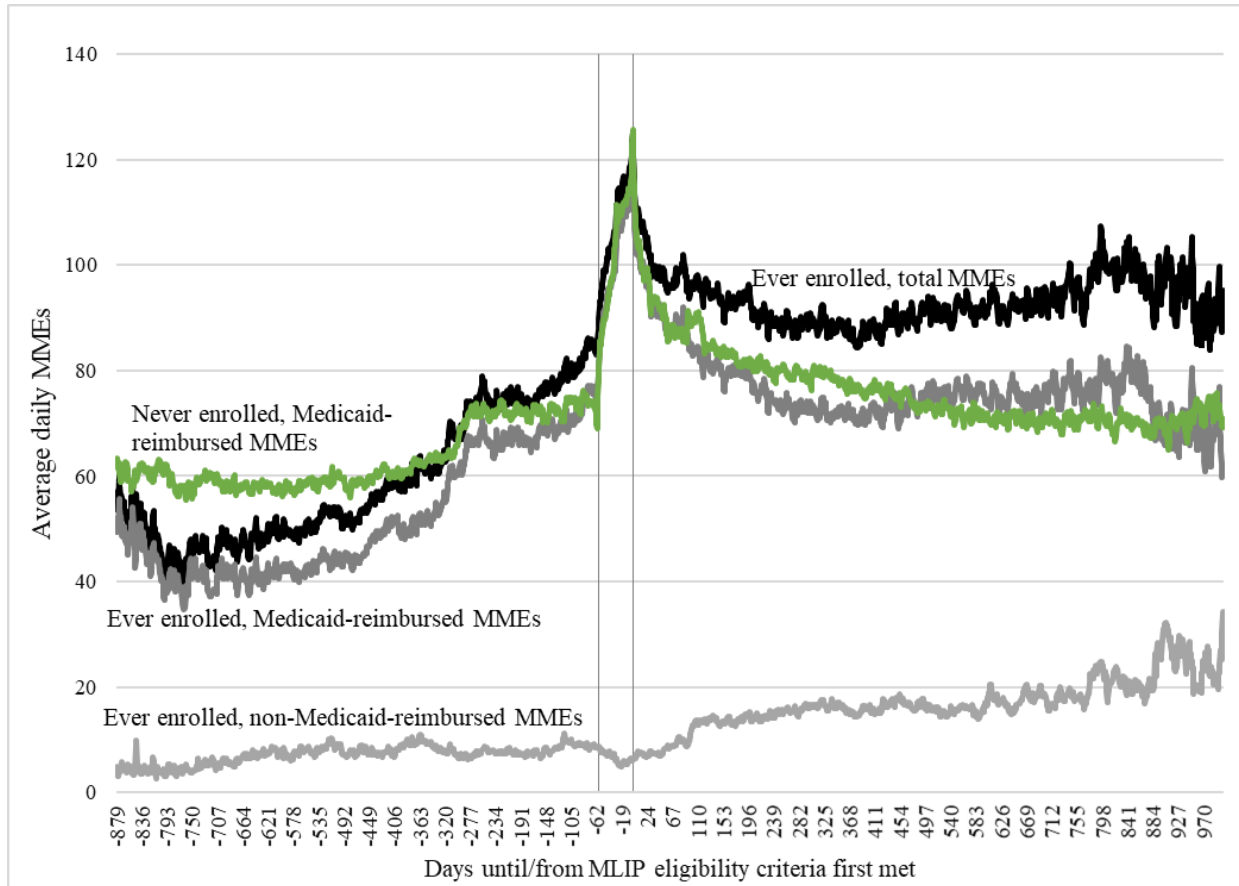
Note: MLIP-eligibility criteria defined as receiving >6 opioid or benzo prescriptions in a 2-month period. MLIP prescriber criterion could not be evaluated in the data available. See Section 5.5 for more information.

APPENDIX B—DETAILS ON COVARIATE CATEGORIES AND CLAIMS-RELATED CODES USED TO DEFINE BENEFICIARY CHARACTERISTICS

DEMOGRAPHICS	
Age	Continuous variable. Measured at time of Medicaid lock-in program (MLIP) enrollment in years.
Gender	Male or female. Measured at time of MLIP enrollment.
Race	White, black, or other. "Other" included Asian, Hispanic, American Indian, Pacific Islander or Native, among others. Measured at time of MLIP enrollment.
Urbanicity of county of residence	The U.S. Department of Agriculture's 2013 rural-urban continuum codes were used to classify counties according to urbanicity. This classification system assigns categories to metropolitan counties based on their population size and assigns categories to nonmetropolitan counties based on their degree of urbanization and how close they are to a metropolitan area; there are nine categories. These nine categories were collapsed to four in our analysis: 1) counties in metropolitan areas of greater than or equal to 1 million people; 2) counties in metropolitan areas of less than 1 million people; 3) non-metropolitan, urban counties with a population of greater than or equal to 20,000 people; and 4) non-metropolitan, urban counties with a population of less than 20,000 people or rural counties. For more information, see: https://www.ers.usda.gov/data-products/rural-urban-continuum-codes/. County of residence was measured at time of MLIP enrollment.
Overdose death rate in county of residence	County overdose death rates were obtained from the North Carolina (NC) Division of Public Health. Death rates were averaged over the period of 2008 through 2013 and counties were grouped into quintiles according to their average rate. Death rates were reported as per 100,000 population per year, and categories were defined as: 20.0-32.2; 15.0-19.9; 11.1-14.9; 8.7-11.0; and 2.6-8.6. County of residence was measured at time of MLIP enrollment.
Medicaid eligibility category code	Medicaid eligibility categories provide information on criteria met to qualify for Medicaid benefits. Medicaid benefits are available to NC residents who are pregnant and have household incomes up to 196% of the federal poverty level; parents who have dependent children and have a household income up to 45% of the federal poverty level (e.g., for a family of three, income cannot exceed $667/month); blind persons; and persons under the age of 65 years who are unable to work due to a severe disability that is expected to last at least 12 months. In our analysis, categories were collapsed and defined as: 1) aid to families with dependent children; 2) aid to disabled; and 3) aid for other reasons (e.g., blind, pregnant women). For more information, see: https://dma.ncdhhs.gov/medicaid/get-started/eligibility-for-medicaid-or-health-choice. Measured at time of MLIP enrollment.

Medicaid class code	Class codes provide further information on Medicaid qualification. Most Medicaid beneficiaries qualify for Medicaid under a "categorically needy" class code, indicating that certain income requirements were met as determined by the specific aid category (e.g., families with dependent children, disabled). However, other routes through which individuals may qualify include a "medically needy" classification in which a person may have not satisfied financial eligibility requirements (i.e., their income was too high) but significant medical expenses reduced their income below a certain level that then qualified them as "medically needy." For more information, see: https://dma.ncdhhs.gov/medicaid/get-started/eligibility-for-medicaid-or-health-choice. Measured at time of MLIP enrollment.
SUBSTANCE USE-RELATED	
Alcohol-related disorder	Used Agency for Healthcare Research and Quality's (AHRQ) Clinical Classification Software (CCS) definition. Required at least 1 inpatient or 2 non-inpatient claims with specific ICD-9-CM diagnosis codes that appear more than once over a time span exceeding 30 days. Specific codes included: 291.0, 291.1, 291.2, 291.3, 291.4, 291.5, 291.8, 291.81, 291.82, 291.89, 291.9, 303.00, 303.01, 303.02, 303.03, 303.90, 303.91, 303.92, 303.93, 305.00, 305.01, 305.02, 305.03, 357.5, 425.5, 535.3, 535.30, 535.31, 571.0, 571.1, 571.2, 571.3, 760.71, 980.0. For more information, see: https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Measured using a one-year lookback period from time of MLIP enrollment.
Other substance-related disorder	Used AHRQ's CCS definition. Required at least 1 inpatient or 2 non-inpatient claims with specific ICD-9-CM diagnosis codes that appear more than once over a time span exceeding 30 days. Specific codes included: 292.0, 292.11, 292.12, 292.2, 292.81, 292.82, 292.83, 292.84, 292.85, 292.89, 292.9, 304.00, 304.01, 304.02, 304.03, 304.10, 304.11, 304.12, 304.13, 304.20, 304.21, 304.22, 304.23, 304.30, 304.31, 304.32, 304.33, 304.40, 304.41, 304.42, 304.43, 304.50, 304.51, 304.52, 304.53, 304.60, 304.61, 304.62, 304.63, 304.70, 304.71, 304.72, 304.73, 304.80, 304.81, 304.82, 304.83, 304.90, 304.91, 304.92, 304.93, 305.20, 305.21, 305.22, 305.23, 305.30, 305.31, 305.32, 305.33, 305.40, 305.41, 305.42, 305.43, 305.50, 305.51, 305.52, 305.53, 305.60, 305.61, 305.62, 305.63, 305.70, 305.71, 305.72, 305.73, 305.80, 305.81, 305.82, 305.83, 305.90, 305.91, 305.92, 305.93, 648.30, 648.31, 648.32, 648.33, 648.34, 655.50, 655.51, 655.53, 760.72, 760.73, 760.75, 779.5, 965.00, 965.01, 965.02, 965.09, V65.42. For more information, see: https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Measured using a one-year lookback period from time of MLIP enrollment.
Medication-assisted treatment	Any prescription claim for a buprenorphine product indicated for use of opioid addiction treatment (i.e., medication assisted treatment) or any mention of Current Procedural Terminology (CPT) code H0020,

Medication or drug-related overdose	"Alcohol and/or drug services; methadone administration and/or service (provision of the drug by a licensed program)." Measured using a one-year lookback period from time of MLIP enrollment. Used ICD-9-CM definition for medication and drug-related overdoses developed by the NC Division of Public Health, in collaboration with the University of North Carolina's Injury Prevention Research Center, through a Centers for Disease Control and Prevention-funded surveillance quality improvement initiative to improve injury surveillance for outcomes, such as overdoses. Definitions were developed using existing state and national organization definitions; advice from content experts in injury epidemiology, surveillance methods, and public health informatics; and end user feedback. Definition included any mention of the following ICD-9-CM diagnosis codes 960-979 or e-codes E850-E858, E950.0-E950.5, E962.0, E980.0-E980.5. For more information, see: http://www.injuryfreenc.ncdhhs.gov/DataSurveillance/Poisoning.htm. Measured using a one-year lookback period from time of MLIP enrollment.

HEALTH CARE UTILIZATION

Number of unique pharmacies from which Medicaid-reimbursed prescriptions were obtained	Includes all unique pharmacies that a beneficiary visited in the year prior to enrollment in the lock-in program, according to Medicaid claims data. We did not have reliable information on pharmacies visited using Controlled Substances Reporting System (CSRS) records.
Maximum number of unique pharmacies from which Medicaid-reimbursed prescriptions were obtained in 1 month	Provides information on the maximum number of unique pharmacies visited in a one calendar month period in the year prior to enrollment in the MLIP, according to Medicaid claims data. We did not have reliable information on pharmacies visited using CSRS records.
Emergency department visits	Claims with the following revenue center codes RC450, RC451, RC456, RC459, RC981 or Current Procedural Terminology (CPT) codes 99281-99285 were flagged as emergency department-related. Multiple claims with the same header start date, header end date, and/or service date for a given beneficiary were counted only once to obtain a total number of *unique* emergency department visits (i.e., to avoid double-counting visits). Measured using a one-year lookback period from time of MLIP enrollment.
Inpatient admissions	Unique inpatient admissions were summed across the year prior to MLIP enrollment. Claims with a place of service code= "inpatient" were counted. Multiple claims with the same header start date, header end date, and/or service date for a given beneficiary were counted

	once only to obtain a total number of inpatient admissions (i.e., to avoid double-counting).
Days with Medicaid coverage	Using information from beneficiaries' Medicaid eligibility files, summed the number of days in the year prior to MLIP enrollment in which each beneficiary had Medicaid coverage.

PAIN-RELATED DIAGNOSES

Any joint pain of arthritis	Required any mention of specific ICD-9-CM diagnosis codes: >=710 and <720 or >=725 and <740. See: Sullivan MD, Edlund MJ, Fan M-Y, et al. Trends in use of opioids for non-cancer pain conditions 2000-2005 in Commercial and Medicaid insurance plans: The TROUP study. *Pain* 2008;138:440-449 for additional details. Measured using a one-year lookback period from time of MLIP enrollment.
Back pain	Required any mention of specific ICD-9-CM diagnosis codes: 721.3x–721.9x, 722.2x, 722.30, 722.70, 722.80, 722.90, 722.32, 722.72, 722.82, 722.92, 722.33, 722.73, 722.83, 722.93, 724.xx, 737.1, 737.3, 738.4, 738.5, 739.2, 739.3, 739.4, 756.10, 756.11, 756.12, 756. 13, 756.19, 805.4, 805.8, 839.2, 839.42, 846, 846.0, 847.1, 847.3, 847.2, 847.9. See: Sullivan MD, Edlund MJ, Fan M-Y, et al. Trends in use of opioids for non-cancer pain conditions 2000-2005 in Commercial and Medicaid insurance plans: The TROUP study. *Pain* 2008;138:440-449 for additional details. Measured using a one-year lookback period from time of MLIP enrollment.
Neck pain	Required any mention of specific ICD-9-CM diagnosis codes: 721.0X, 721.1X, 722.0X, 722.31, 722.71, 722.81, 722.91, 723.XX, 839.0, 839.1, 847.0. See: Sullivan MD, Edlund MJ, Fan M-Y, et al. Trends in use of opioids for non-cancer pain conditions 2000-2005 in Commercial and Medicaid insurance plans: The TROUP study. *Pain* 2008;138:440-449 for additional details. Measured using a one-year lookback period from time of MLIP enrollment.
Headache/migraine pain	Required any mention of specific ICD-9-CM diagnosis codes: >=346 and <347, or 307.81. See: Sullivan MD, Edlund MJ, Fan M-Y, et al. Trends in use of opioids for non-cancer pain conditions 2000-2005 in Commercial and Medicaid insurance plans: The TROUP study. *Pain* 2008;138:440-449 for additional details. Measured using a one-year lookback period from time of MLIP enrollment.
Fibromyalgia, chronic pain, or fatigue	Centers for Medicare & Medicaid Services' (CMS) Chronic Conditions Data Warehouse definition used. Definition required at least 1 inpatient or 2 non-inpatient claims with specific ICD-9 diagnosis codes appearing more than once over a time span exceeding 30 days. Specific codes included: 338.2, 338.21, 338.22, 338.23, 338.29, 338.3, 338.4, 780.7, 780.71, 729.1, 729.2. For more information, see: https://www.ccwdata.org/web/guest/condition-categories. Measured using a one-year lookback period from time of MLIP enrollment.

Rheumatoid arthritis or osteoarthritis	Used Centers for Medicare & Medicaid Services' (CMS) Chronic Conditions Data Warehouse (CCW) definition with slight modification. Required at least 1 inpatient or 2 non-inpatient claims with specific ICD-9-CM diagnosis codes appearing more than once over a time span exceeding 30 days. Specific codes included: 714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 720.0, 721.0, 721.1, 721.2, 721.3, 721.90, 721.91. For more information, see: https://www.ccwdata.org/web/guest/condition-categories. Measured using a one-year lookback period from time of MLIP enrollment.
Sickle cell	Used definition consistent with AHRQ's CCS and the previous research (see: Reeves S, Garcia E, Kleyn M, et al. Identifying sickle cell disease cases using administrative claims. *Academic Pediatrics* 2014;14(5 Suppl):S61-67.). Required at least 1 inpatient or 2 non-inpatient claims with specific ICD-9 diagnosis codes that appear more than once over a time span exceeding 30 days. Specific codes included: 28241 28242 28260 28261 28262 28263 28264 28268 28269. Measured using a one-year lookback period from time of MLIP enrollment.
MENTAL HEALTH-RELATED DIAGNOSES	
Depression	Used CMS CCW definition. Required at least 1 inpatient, skilled nursing facility, home health agency, hospital outpatient, or service/carrier claims with specific ICD-9-CM diagnosis codes. Specific codes included: 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 300.4, 311, V79.0. For more information, see "Original CCW Chronic Condition Algorithms" found at: https://www.ccwdata.org/web/guest/condition-categories. Measured using a one-year lookback period from time of MLIP enrollment.
Anxiety disorder	Used CMS CCW definition. Required at least 1 inpatient or 2 non-inpatient claims with specific ICD-9 diagnosis codes appearing more than once over a time span exceeding 30 days. Specific codes included: 293.84, 300.00, 300.01, 300.02, 300.09, 300.10, 300.20, 300.21, 300.22, 300.23, 300.29, 300.3, 300.5, 300.89, 300.9, 308.0, 308.1, 308.2, 308.3, 308.4, 308.9, 309.81, 313.0, 313.1, 313.21, 313.22, 313.3, 313.82, 313.83. For more information, see: https://www.ccwdata.org/web/guest/condition-categories. Measured using a one-year lookback period from time of MLIP enrollment.
Other serious mental health disorder (includes bipolar,	Used CMS CCW definitions. Required at least 1 inpatient or 2 non-inpatient claims with specific ICD-9 diagnosis codes appearing more than once over a time span exceeding 30 days. Specific codes included: 293.81, 293.82, 295.00, 295.01, 295.02, 295.03, 295.04,

personality, schizophrenia or other psychotic, and post-traumatic stress disorders)	295.05, 295.10, 295.11, 295.12, 295.13, 295.14, 295.15, 295.20, 295.21, 295.22, 295.23, 295.24, 295.25, 295.30, 295.31, 295.32, 295.33, 295.34, 295.35, 295.40, 295.41, 295.42, 295.43, 295.44, 295.45, 295.50, 295.51, 295.52, 295.53, 295.54, 295.55, 295.60, 295.61, 295.62, 295.63, 295.64, 295.65, 295.70, 295.71, 295.72, 295.73, 295.74, 295.75, 295.80, 295.81, 295.82, 295.83, 295.84, 295.85, 295.90, 295.91, 295.92, 295.93, 295.94, 295.95, 296.00, 296.01, 296.02, 296.03, 296.04, 296.05, 296.06, 296.10, 296.11, 296.12, 296.13, 296.14, 296.15, 296.16, 296.40, 296.41, 296.42, 296.43, 296.44, 296.45, 296.46, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.7, 296.80, 296.81, 296.82, 296.89, 296.90, 296.99, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9, 298.0, 298.1, 298.2, 298.3, 298.4, 298.8, 298.9, 301.0, 301.10, 301.11, 301.12, 301.13, 301.20, 301.21, 301.22, 301.3, 301.4, 301.50, 301.51, 301.59, 301.6, 301.7, 301.81, 301.82, 301.83, 301.84, 301.89, 301.9, 309.81. For more information, see: https://www.ccwdata.org/web/guest/condition-categories. Measured using a one-year lookback period from time of MLIP enrollment.
OTHER COMORBID CONDITIONS	
Mean Charlson comorbidity index	The Charlson Comorbidity Index (CCI) is a method of categorizing comorbidities based on ICD codes. Each comorbidity is associated with a weight (from 1 to 6), and weights are based on the adjusted risk of mortality or resource use. CCI scores are calculated by summing an individual's weights; a score of zero indicates no comorbidities were detected. We used Quan's enhanced CCI macro which looks at 17 comorbidities. An individual comorbidity was considered present if there was at least 1 inpatient or 2 non-inpatient claims with the specific ICD-9 diagnosis codes that appeared more than once over a time span exceeding 30 days. Additional details on the index and specific comorbidities included can be found in: Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care* 2005;43(11):1130-1139.
Cancer	Used Quan et al., 2005 definition. Required at least 1 inpatient or 2 non-inpatient claims with specific ICD-9 diagnosis codes appearing more than once over a time span exceeding 30 days. Specific codes included: 140-165, 170-172, 174-176, 179-208, 238.6. Additional details can be found in: Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care* 2005;43(11):1130-1139.

APPENDIX C—TEMPORAL TREND MEASURE CONSTRUCTION FOR AIM 1 ANALYSES

Temporal trends over calendar time exist in the overall population in terms of access to opioids and related effects. To help for confounding due to temporal changes over calendar time, we developed a set of temporal trend measures. These temporal trend measures were included in all models. We generated these measures from temporal trends in outcome measures in the population of Medicaid beneficiaries who were eligible to enter the LIP, but who were not enrolled. The creation of temporal trend measures occurred in five steps:

1. We assigned a "program day" (e.g., MLIP day #-1 for the day prior to MLIP enrollment, MLIP day #0 for the first day of lock-in) for each day that a beneficiary was in our study.

2. We extracted the calendar month and year underlying that "program day." For example, one person's first day in the MLIP might have been 11/1/2010 (11/2010 would have been extracted) and another's might have been 5/1/2012 (5/2012 would have been extracted).

3. We constructed a cohort of Medicaid beneficiaries eligible for MLIP enrollment, according to MLIP enrollment criteria, but never enrolled during the study period. We identified the MLIP-eligible population by examining Medicaid-reimbursed prescription fills from June 2010 through December 2012 to determine who would have been eligible for MLIP enrollment when the program began in October 2010 through the end of our dataset in June 2013. For each two calendar month period, we examined the number of opioid and benzodiazepine prescriptions obtained by each beneficiary. Consistent with MLIP eligibility criteria, beneficiaries with more than six

opioid or benzodiazepine prescriptions in a consecutive two-month period were defined as MLIP-eligible. While beneficiaries could also become eligible by obtaining these prescriptions from more than three unique prescribers, the data available did not provide accurate information on numbers of unique prescribers. Therefore, we were unable to use the third criterion in constructing our MLIP-eligible population. However, given that almost all of the MLIP-enrolled cohort met the first criterion (i.e., more than six opioid prescriptions) and given that there were likely relatively few people who visited several unique prescribers but did not also meet the prescription thresholds, we would not expect this missing information to have excluded many beneficiaries.

4. We calculated the mean of each outcome measure for each calendar month and year combination within the eligible but never MLIP-enrolled cohort.

5. We matched the mean of each calendar month/year in the never MLIP-enrolled cohort to the calendar month/year represented within each "program day" of our MLIP-enrolled study cohort. Ultimately, we generated a temporal trend measure that allowed us to disentangle changes in outcomes occurring over calendar time from changes occurring over MLIP "program time" by controlling for changes in outcome measures over calendar time in a similar but never MLIP-enrolled population.

APPENDIX D—CRITERIA USED TO DETERMINE NUMBER OF MEANINGFUL TRAJECTORY CLASSES IN LATENT CLASS GROWTH ANALYSES AND MODEL SELECTION PROCESS

All LCGA models were fit in Mplus, version 7.4, using robust maximum likelihood estimation (MLR). Since research shows that the maximum likelihood function for finite mixture models is prone to settling on local maxima solutions, all models were fit using several maximum likelihood start values.[160,187] We specified that models begin with 100 random starts, optimizing the best 20, and we confirmed that the best log-likelihood values were duplicated across start values.

To determine the number of meaningful trajectory classes, we used several criteria: likelihood ratio tests (LRT), information criteria, measures of entropy, class size, and interpretability.[160] The Lo-Mendell-Rubin LRT was used to compare models with j trajectory classes as compared to $j+1$ trajectory classes with a statistical cutpoint set at $\alpha=0.05$.[188] Test statistics with corresponding p-values less than 0.05 led us to favor the model with $j+1$ trajectory groups. We used Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), and sample-size adjusted BIC (ssBIC) to assess model fit; models with lower information criteria were favored over those with higher criteria. Entropy, a measure of latent class separation that ranges from 0 to 1, was also considered.[189] A larger entropy value indicates better separation, and models with entropy values greater than 0.8 are generally regarded as having high and suitable entropy.[190] Finally, as a guide to our final model choice we considered general interpretability and class size, with no class having less than a 5% prevalence to avoid unstable or obscure classes.

The five class solution was ultimately selected as the best solution (see Table below). As commonly observed[191], the AIC, BIC, and ssBIC improved with the addition of each class;

however, only marginal gains were observed after the addition of the fourth or fifth class. The

Lo-Mendell-Rubin LRT favored up to a six class solution, as did estimates of the smallest class

size. Models specified with seven and eight classes were associated with smallest class sizes that

were potentially indicative of unstable or obscure class solutions. Graphical comparisons

between the five and six class solutions revealed that for the six class solution, there were strong

similarities between two of the trajectory classes (i.e., parallel lines with a slight level shift).

Therefore, the five class solution was selected as the best overall solution, and was determined to

achieve the best balance of comprehensiveness with interpretability and parsimony.

TABLE. Model fit statistics for linear piecewise latent class growth analysis model estimating

trajectories in the log of average daily morphine milligram equivalents (MMEs) of opioids

dispensed to beneficiaries enrolled in the North Carolina Medicaid "lock-in" program per month

Latent classes	AIC	BIC	ssBIC	Lo-Mendell-Rubin LRT p-value	Entropy	Smallest class size
1	418,435	418,477	418,454	N/A	N/A	N/A
2	367,304	367,393	367,345	<0.001	0.98	0.42
3	348,124	348,259	348,186	0.012	0.98	0.18
4	338,468	338,651	338,553	0.016	0.97	0.11
5	330,825	331,055	330,931	0.006	0.97	0.13
6	324,640	324,918	324,769	0.026	0.97	0.11
7	319,866	320,190	320,015	0.306	0.97	0.05
8	316,638	317,010	316,810	0.251	0.97	0.04

Note: model specified with five linear pieces
AIC= Akaike's Information Criterion; BIC= Bayesian Information Criterion; ssBIC=sample-size adjusted
BIC; LRT= likelihood ratio test

APPENDIX E—CALCULATION OF STANDARDIZED DIFFERENCES

Standardized differences provide a measure of the similarity or dissimilarity of two groups with respect to specific covariates. For continuous and binary covariates, standardized differences were used to compare the means of two groups in units of the pooled standard deviation of the two groups. For categorical variables with more than two levels, an overall standardized difference was calculated, using a multivariate Mahalanobis distance method.[168] In order to calculate standardized differences, we assigned beneficiaries to the class for which they had the highest posterior probability of belonging. While this method, known as modal assignment, has been criticized for removing the uncertainty of latent classification,[192,193] the classification uncertainty for most beneficiaries in our cohort was very small (see Table below). As an additional check, we recalculated the counts, percentages, and means shown in Table 7.1, using modal assignment instead of posterior probability weights and found very little difference. Therefore, any error introduced by modal assignment to calculate standardized differences was likely minimal.

TABLE. Average latent class probabilities for most likely latent class membership

Most likely latent class	Mean	Standard deviation	25th percentile	Median	75th percentile
1	0.993	0.049	1.000	1.000	1.000
2	0.979	0.069	0.999	1.000	1.000
3	0.968	0.090	0.996	1.000	1.000
4	0.969	0.084	0.996	1.000	1.000
5	0.989	0.053	1.000	1.000	1.000

APPENDIX F—SENSITIVITY ANALYSES OF TRAJECTORIES OF OPIOID DOSAGES (MEASURED IN MORPHINE MILIGRAM EQUIVALENTS (MMEs)) DISPENSED TO BENEFICIARIES ELIGIBLE FOR THE NORTH CAROLINA MEDICAID "LOCK-IN" PROGRAM (MLIP) BUT NEVER ENROLLED

<u>Sensitivity Analysis Methods</u>

To examine the extent to which opioid dispensing trajectory findings were unique to beneficiaries enrolled in the MLIP (and potentially influenced by the MLIP), we fit similar models in a MLIP-eligible, but never enrolled cohort. Details on the formation of an eligible but never MLIP-enrolled cohort, as well as characteristics of these beneficiaries were previously reported in Chapter 5.

Previous analyses of MLIP-eligible and enrolled and MLIP-eligible and never enrolled cohorts revealed a similar overall pattern in average daily MMEs prior to and immediately following the point at which MLIP eligibility criteria were met.[175] Specifically, both MLIP-enrolled and never enrolled cohorts exhibited an escalation in average daily MMEs, triggering of MLIP criteria, and a nearly equal de-escalation in MMEs (regardless of enrollment in the MLIP). Because of these similarities, we were interested in examining whether potential underlying heterogeneity in trajectories for these two cohorts was also similar, which could provide some indication of the extent to which the MLIP influenced trajectory patterns.

Using a five piece, linear piecewise LCGA model specification similar to the model chosen for our MLIP-enrolled cohort, we examined the extent to which trajectory patterns, prevalences of patterns, and covariate associations with patterns in the never enrolled cohort were consistent with those in the MLIP-enrolled cohort.

<u>Sensitivity Analysis Results</u>

Sensitivity analyses in the similar, but never MLIP-enrolled, cohort of Medicaid beneficiaries revealed similar trajectory patterns and pattern prevalences (Figure F). While the

actual prevalences of many covariates differed, covariate associations with patterns were generally similar between the MLIP-enrolled and never enrolled cohorts (Table F). For example, among the MLIP-enrolled, the prevalences of rheumatoid arthritis or osteoarthritis by class were 41%, 39%, 29%, 26%, and 12% for classes 1 to 5, respectively (Table 7.1). Among those eligible but never enrolled, prevalences were 29%, 27%, 23%, 16%, and 8% for classes 1 to 5, indicating different prevalence levels but similar associations with class (Table F). Notable differences in covariate associations included history of MAT and cancer diagnoses. History of MAT was strongly associated with class among the enrolled but not among the never enrolled. Overall prevalences of cancer were much higher in the never enrolled than enrolled.

Sensitivity Analysis Limitations

Two limitations to this analysis should be noted: 1) we did not have CSRS records on those who were not enrolled, only Medicaid claims and 2) the time axis inevitably differed from our primary analysis. In our primary analysis, the MLIP-enrolled cohort was examined from time until/from MLIP enrollment; however, the never enrolled cohort could only be examined using time until/from first meeting MLIP eligibility criteria. Further analyses that 1) constrained MLIP-enrolled models to only Medicaid-reimbursed MMEs and 2) altered the time axis in MLIP-enrolled models to time until/from first meeting MLIP eligibility criteria revealed that findings were not sensitive to these two limitations.

FIGURE F. Trajectories of log of average daily morphine milligram equivalents (MMEs) of opioids dispensed* per month to beneficiaries eligible for the North Carolina Medicaid "lock-in" program but **never enrolled**, October 2009-June 2013 (n=11,600)
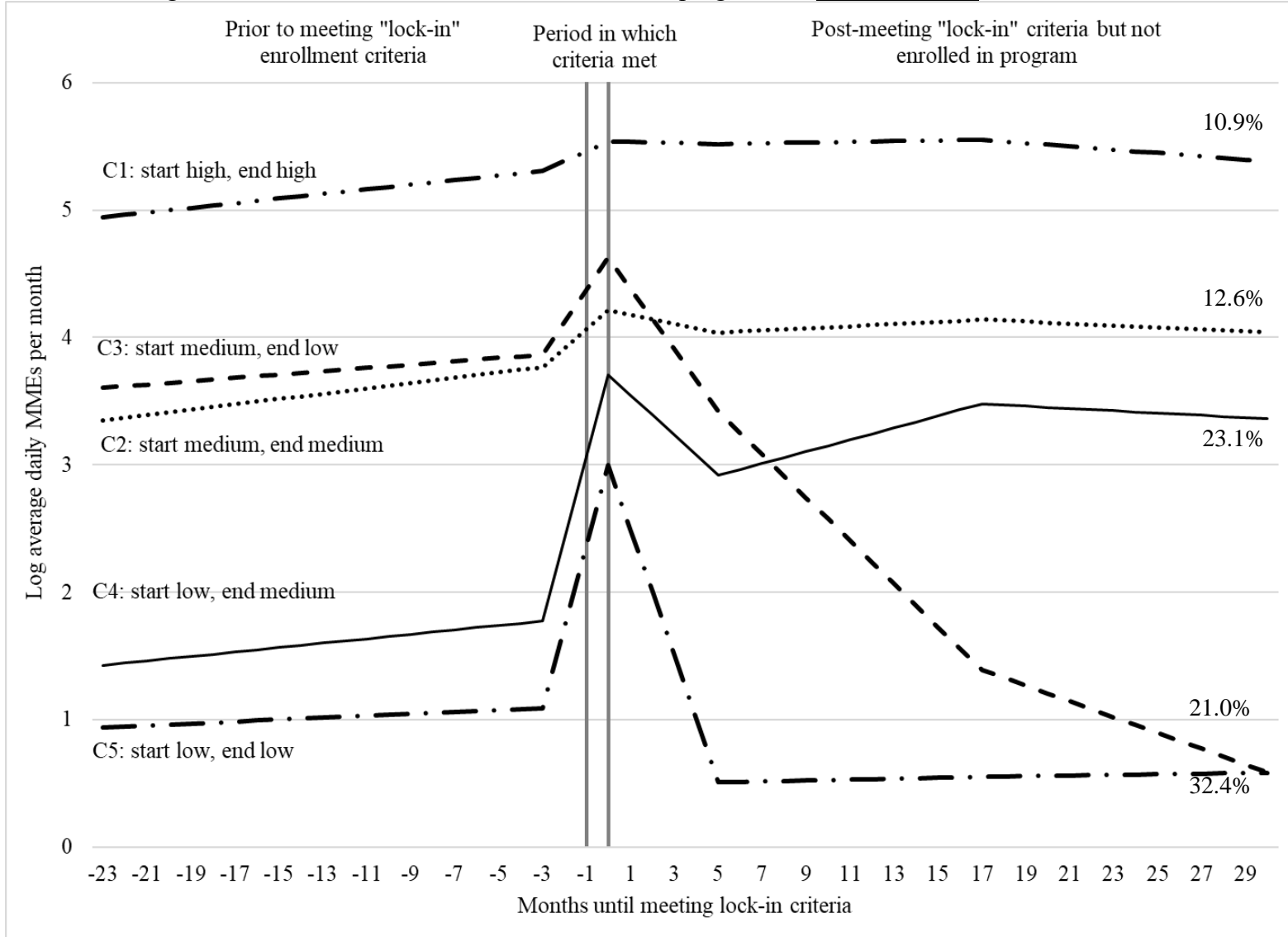
* Only from Medicaid-reimbursed opioid prescriptions.

TABLE F. Weighted* counts, percentages, and means for characteristics of each of the five latent classes representing different trajectories in the log of average daily morphine milligram equivalents (MME) of opioids dispensed[#] to beneficiaries eligible for the North Carolina Medicaid "lock-in" program but **never enrolled**, October 2009-June 2013 (n=11,600)

	Start high, end high (C1) (n=1,272; 10.9%)*	Start medium, end medium (C2) (n=1,484; 12.6%)*	Start medium, end low (C3) (n=2,415; 21.0%)*	Start low, end medium (C4) (n=2,633; 23.1%)*	Start low, end low (C5) (n=3,796; 32.4%)*
	N (%) for categorical variables; Mean (25th pct, median, 75th pct) for continuous variables				
DEMOGRAPHICS^					
Age (years)	46.5 (39, 48, 55)	45.2 (37, 46, 54)	43.8 (36, 45, 53)	40.0 (31, 39, 49)	35.6 (26, 33, 43)
Gender					
Women	728.7 (57.8)	901.8 (61.7)	1,393.6 (57.1)	1,781.7 (66.5)	2,567.2 (68.3)
Men	533.0 (42.2)	560.3 (38.3)	1,046.2 (42.9)	896.8 (33.5)	1,190.8 (31.7)
Race					
White	993.0 (78.7)	1,050.5 (71.9)	1,803.6 (73.9)	1,996.4 (74.5)	2,841.5 (75.6)
Black	184.1 (14.6)	315.4 (21.6)	516.3 (21.2)	552.9 (20.6)	748.3 (19.9)
Other	84.7 (6.7)	96.1 (6.6)	119.9 (4.9)	129.1 (4.8)	168.2 (4.5)
Urbanicity of county of residence					
Counties in metro areas of ≥ 1 million population	276.2 (21.9)	303.3 (20.8)	571.8 (23.4)	627.9 (23.4)	873.8 (23.3)
Counties in metro areas of < 1 million population	556.7 (44.1)	698.2 (47.8)	1,126.4 (46.2)	1,215.8 (45.4)	1,763.9 (46.9)
Nonmetro, urban population of ≥ 20,000	235.7 (18.7)	266.0 (18.2)	399.7 (16.4)	495.1 (18.5)	611.5 (16.3)
Nonmetro, urban population of <20,000 or rural population	193.2 (15.3)	194.5 (13.3)	340.7 (14.0)	339.5 (12.7)	504.1 (13.4)

Overdose death rate in county of residence (per 100,000 person-years)					
20.0-32.2	245.8 (19.5)	281.5 (19.3)	500.0 (20.5)	552.5 (20.6)	755.2 (20.1)
15.0-19.9	230.7 (18.3)	345.4 (23.6)	625.8 (25.7)	738.0 (27.6)	1,078.0 (28.7)
11.1-14.9	324.6 (25.7)	341.4 (23.4)	486.3 (19.9)	508.5 (19.0)	704.2 (18.7)
8.7-11.0	273.6 (21.7)	326.9 (22.4)	504.5 (20.7)	552.1 (20.6)	763.8 (20.3)
2.6-8.6	187.0 (14.8)	166.8 (11.4)	322.0 (13.2)	327.0 (12.2)	452.2 (12.0)
Medicaid eligibility category code					
Aid to families with dependent children	361.4 (28.6)	590.6 (40.4)	935.0 (38.3)	1,558.1 (58.2)	2,357.9 (62.7)
Aid to disabled	897.4 (71.1)	855.5 (58.5)	1,480.7 (60.7)	1,045.3 (39.0)	1,140.1 (30.3)
Aid for other reasons (e.g., aid to blind, aid to pregnant women)	3.0 (0.2)	15.9 (1.1)	24.1 (1.0)	74.0 (2.8)	259.9 (6.9)
Medicaid class code					
Categorically needy	1,195.3 (94.7)	1,353.9 (92.6)	2,151.1 (88.2)	2,441.8 (91.2)	3,416.0 (90.9)
Medically needy	58.8 (4.7)	103.5 (7.1)	270.5 (11.1)	223.9 (8.4)	321.3 (8.6)
Other	7.6 (0.6)	4.7 (0.3)	18.2 (0.8)	12.8 (0.5)	20.6 (0.6)
SUBSTANCE USE-RELATED †					
Alcohol-related disorder	58.8 (4.7)	97.4 (6.7)	205.0 (8.4)	189.1 (7.1)	220.7 (5.9)
Other substance-related disorder	208.5 (16.5)	187.2 (12.8)	419.8 (17.2)	345.1 (12.9)	405.3 (10.8)
Medication-assisted treatment (MAT)	29.5 (2.3)	15.7 (1.1)	79.3 (3.3)	59.5 (2.2)	66.1 (1.8)
Medication or drug-related overdose	55.6 (4.4)	45.6 (3.1)	95.5 (3.9)	94.9 (3.5)	114.5 (3.1)
HEALTH CARE UTILIZATION †					
Emergency department visits	2.5 (0, 1, 3)	3.6 (1, 2, 5)	4.2 (1, 2, 5)	4.7 (1, 3, 6)	4.7 (1, 3, 6)
Inpatient admissions	1.0 (0, 0, 1)	1.1 (0, 1, 1)	1.4 (0, 1, 2)	1.0 (0, 0, 1)	0.8 (0, 0, 1)
Days with Medicaid coverage	329.6 (365, 365, 365)	311.3 (275, 365, 365)	311.3 (273, 365, 365)	307.1 (273, 365, 365)	295.4 (242, 365, 365)

PAIN-RELATED DIAGNOSES †					
Any joint pain or arthritis	1,079.7 (85.6)	1,290.6 (88.3)	2,046.6 (83.9)	2,205.3 (82.3)	2,684.7 (71.4)
Back pain	946.4 (75.0)	1,025.5 (70.2)	1,631.9 (66.9)	1,714.4 (64.0)	2,005.7 (53.4)
Neck pain	427.9 (33.9)	451.4 (30.9)	737.6 (30.2)	759.7 (28.4)	775.4 (20.6)
Headache/migraine pain	141.7 (11.2)	229.9 (15.7)	317.0 (13.0)	411.8 (15.4)	500.0 (13.3)
Fibromyalgia, chronic pain, or fatigue	751.8 (59.6)	610.8 (41.8)	1,103.2 (45.2)	780.2 (29.1)	596 (15.9)
Rheumatoid arthritis or osteoarthritis	373.0 (29.6)	403.2 (27.6)	544.4 (22.3)	417.6 (15.6)	294.7 (7.8)
Sickle cell	25.8 (2.0)	10.5 (0.7)	26.3 (1.1)	14.4 (0.5)	9.9 (0.3)
MENTAL HEALTH-RELATED DIAGNOSES †					
Depression	585.8 (46.4)	657.5 (45.0)	1,170.9 (48.0)	1,180.1 (44.1)	1,530.6 (40.7)
Anxiety disorder	353.9 (28.1)	382.4 (26.2)	633.8 (26.0)	673.3 (25.1)	797.7 (21.2)
Other serious mental health disorder (includes bipolar, personality, schizophrenia or other psychotic, and post-traumatic stress disorders)	147.5 (11.7)	232.0 (15.9)	407.4 (16.7)	427.9 (16.0)	644.2 (17.1)
OTHER COMORBID CONDITIONS †					
Mean Charlson co-morbidity index	2.3 (0, 1, 3)	1.7 (0, 1, 3)	2.8 (0, 1, 4)	1.5 (0, 0, 2)	0.9 (0, 0, 1)
Cancer	244.2 (19.4)	186.3 (12.7)	604.5 (24.8)	314.0 (11.7)	230.9 (6.1)

pct= percentile; C= class

* Weights are estimated posterior probabilities for belonging to a given class

Only includes opioids dispensed and paid for through Medicaid reimbursement

^ Assessed at the time of "lock-in" program enrollment

† Assessed using a one-year lookback period from the date of "lock-in" program enrollment

REFERENCES

1.   Centers for Disease Control and Prevention. Wide-ranging Online Data for Epidemiologic Research: National Vital Statistics System mortality data. 2016.

2.   Substance Abuse and Mental Health Services Administration. Highlights of the 2011 Drug Abuse Warning Network (DAWN) findings on drug-related emergency department visits. The DAWN Report. 2013.

3.   Florence CS, Zhou C, Luo F, Xu L. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. *Medical Care.* 2016;54(10):901-906.

4.   North Carolina State Center for Health Statistics. Vital Statistics- Deaths. 2015.

5.   North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT). North Carolina Emergency Department Visits. 2015.

6.   North Carolina State Center for Health Statistics. Vital Statistics- Hospitalizations. 2015.

7.   North Carolina Department of Health and Human Services. Medicaid Income and Resources Requirements. 2017.

8.   Zerzan JT, Morden NE, Soumerai S, et al. Trends and geographic variation of opiate medication use in state Medicaid fee-for-service programs, 1996 to 2002. *Medical Care.* 2006;44(11):1005-1010.

9.   Braden JB, Fan MY, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Trends in use of opioids by noncancer pain type 2000-2005 among Arkansas Medicaid and HealthCore enrollees: results from the TROUP study. *The Journal of Pain.* 2008;9(11):1026-1035.

10.   Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Archives of Internal Medicine.* 2006;166(19):2087-2093.

11.   Freburger JK, Holmes GM, Carey TS. Physician referrals to physical therapy for the treatment of musculoskeletal conditions. *Archives of Physical Medicine and Rehabilitation.* 2003;84(12):1839-1849.

12.   Mack KA, Zhang K, Paulozzi L, Jones C. Prescription practices involving opioid analgesics among Americans with Medicaid, 2010. *Journal of Health Care for the Poor and Underserved.* 2015;26(1):182-198.

13.   Agency for Healthcare Research and Quality (AHRQ). Nationwide Inpatient Sample. 2012.

14.   Agency for Healthcare Research and Quality (AHRQ). Nationwide Emergency Department Sample 2012.

15.   Sharp MJ, Melnik TA. Poisoning deaths involving opioid analgesics - New York State, 2003-2012. *Morbidity and Mortality Weekly Report (MMWR).* 2015;64(14):377-380.

16.   Fernandes JC, Campana D, Harwell TS, Helgerson SD. High mortality rate of unintentional poisoning due to prescription opioids in adults enrolled in Medicaid compared to those not enrolled in Medicaid in Montana. *Drug & Alcohol Dependence.* 2015;153:346-349.

17.   Coolen P, Best S, Lima A, Sabel J, Paulozzi L. Overdose deaths involving prescription opioids among Medicaid enrollees - Washington, 2004-2007. *Morbidity and Mortality Weekly Report (MMWR).* 2009;58(42):1171-1175.

18.   Whitmire JT, Adams GW. Unintentional overdose deaths in the North Carolina Medicaid population: prevalence, prescription drug use, and medical care services. *SCHS Studies: A publication of the State Center for Health Statistics.* 2010;162.

19.   Alexander GC, Frattaroli S, Gielen AC. The prescription opioid epidemic: an evidence-based apporach. *John Hopkins Bloomberg School of Public Health.* 2015.

20.   Haegerich TM, Paulozzi LJ, Manns BJ, Jones CM. What we know, and don't know, about the impact of state policy and systems-level interventions on prescription drug overdose. *Drug & Alcohol Dependence.* 2014;145:34-47.

21.   Centers for Disease Control and Prevention. Prescription drug monitoring programs (PDMPs). 2015.

22.   National Alliance for Model State Drug Laws. Prescription drug monitoring programs. 2015.

23.   National Conference of State Legislatures. Drug overdose immunity "Good Samaritan" laws. 2015.

24.   Wheeler E, Jones TS, Gilbert MK, Davidson PJ. Opioid overdose prevention programs providing naloxone to laypersons-- United States, 2014. *Morbidity and Mortality Weekly Report (MMWR).* 2015;64(23):631-635.

25.   Office of Diversion Control, U.S. Department of Justice. National take-back initiative. 2015.

26.   Grill C. State legislative update: lawmakers address prescribing practices and pill mills. *Bulletin of the American College of Surgeons.* 2013.

27.   U.S. Food and Drug Administration. A brief overview of risk evaluation & mitigation strategies (REMS). 2015.

28.   Franklin G, Sabel J, Jones CM, et al. A comprehensive approach to address the prescription opioid epidemic in washington state: milestones and lessons learned. *American Journal of Public Health.* 2015;105(3):463-469.

29.   Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain- United States, 2016. *Morbidity and Mortality Weekly Report (MMWR).* 2016;65(1):1-49.

30.   Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies--tackling the opioid-overdose epidemic. *The New England Journal of Medicine.* 2014;370(22):2063-2066.

31.   U.S. Department of Health and Human Services: Behavioral Health Coordinating Committee. Addressing prescription drug abuse in the United States: Current activities and future opportunities. 2013.

32.   Moorman-Li R, Motycka CA, Inge LD, Congdon JM, Hobson S, Pokropski B. A Review of Abuse-Deterrent Opioids For Chronic Nonmalignant Pain. *Pharmacy and Therapeutics.* 2012;37(7):412-418.

33.   Roberts AW, Skinner AC. Assessing the present state and potential of Medicaid controlled substance lock-in programs. *Journal of Managed Care Pharmacy.* 2014;20(5):439-446c.

34.   Centers for Disease Control and Prevention. Patient review and restriction programs: lessons learned from state Medicaid programs. *CDC Expert Panel Meeting Report.* 2012.

35.   Blake SG. The impact of the Louisiana Medicaid lock-in program on the process and clinical and economic outcomes of recipient care. *Northeast Louisiana University [Dissertation].* 1997.

36.   Buck JA, Silverman HA. Use of utilization management methods in State Medicaid programs. *Health Care Financing Review.* 1996;17(4):77-86.

37.   Franklin GM, Mai J, Wickizer T, Turner JA, Fulton-Kehoe D, Grant L. Opioid dosing trends and mortality in Washington State workers' compensation, 1996–2002. *American Journal of Industrial Medicine.* 2005;48(2):91-99.

38.   Centers for Medicare and Medicaid Services. Medicaid drug utilization review: state comparison/summary report FFY 2014 annual report-- prescription drug fee-for-service programs. 2015.

39.   U.S. Government Accountability Office. Medicaid: Fraud and abuse related to controlled substances identified in selected states. *GAO-09-957.* 2009.

40.   North Carolina Department of Health and Human Services. Implementation of a Recipient Management Lock-In Program. *Medicaid Bulletin.* 2010;August 2010.

41.   North Carolina Division of Medical Assistance. North Carolina Medicaid Pharmacy Newsletter. 2017;265.

42.   Paulozzi LJ. Prescription drug overdoses: a review. *Journal of Safety Research.* 2012;43(4):283-289.

43.   Singleton TE. Missouri's lock-in: control of recipient misutilization. *Journal for Medicaid Management.* 1977;1(3):10-17.

44.   Keast SL, Nesser N, Farmer K. Strategies aimed at controlling misuse and abuse of opioid prescription medications in a state Medicaid program: a policymaker's perspective. *The American Journal of Drug and Alcohol Abuse.* 2015;41(1):1-6.

45.   Melnikow J, Yang Z, Soulsby M, Ritley D, Kizer K. Approaches to drug overdose prevention analytical tool (ADOPT): evaluating cost and health impacts of a Medicaid patient review & restriction program. 2012.

46.   Chinn FJ. Medicaid recipient lock-in program--Hawaii's experience in six years. *Hawaii Medical Journal.* 1985;44(1):9-18.

47.   Blake SG, Feldhaus JF, Huner TS, Rappaport H, Holt G, Medon PJ. The effect of the Louisiana Medicaid lock-in on prescription drug utilization and expenditures. *Value Health.* 1998;1(1):72.

48.   Hladilek MK, Howe MJ, Carr RM. An overview of Wisconsin Medicaid quality. *Wisconsin Medical Journal: Official Publication of the State Medical Society of Wisconsin.* 2004;103(3):58-62.

49.   Best S. PMP use by Medicaid. 2012.

50.   Best S. Patient review and coordination program. 2012.

51.   Coolen P. Patient review and coordination program for medical assistance clients who need assistance in appropriate use of services (presentation). 2009.

52.   Oklahoma Health Care Authority, Mitchell L. Lock-in program promotes appropriate use of resources. *Provider Update.* 2009.

53.   Colorado Office of the State Auditor. Medicaid prescription drugs. 2015.

54.   Conneticut Medical Assistance Pharmacy Program. Drug utilization review (DUR) program board meeting. 2012.

55.   Conneticut Medical Assistance Pharmacy Program. Drug utilization review (DUR) program board meeting minutes. 2013.

56.   Florida Agency for Health Care Administration. Medicaid prescribed drug program spending control initiatives for the quarter: January 1, 2014-March 31, 2014. 2014.

57.   Florida Medicaid. Medicaid prescribed drug spending control program initiatives: quarterly report January 1- March 31, 2005. 2005.

58. Jordan E. Number of Iowa patients 'locked-in' to single drug sources skyrockets. *The Gazette.* 2014.

59. Colburn D, Coady J, Ellis A, Griffin H, Tripp M. Medicaid integrity report: Iowa comprehensive program integrity review-- Final report. 2008.

60. Hatchett EB. Medicaid's Recipient Lock-In Program: December 1997- Performance Audit. 1997.

61. Amerigroup Real Solutions. Benefits and member management, Section Q: Pharmacy. 2014.

62. Missouri Department of Social Services. MMAC participant lock-in unit report: October 2015. 2015.

63. Chandler T, Sandler BS, Charleston M, Tubbs D, Truman J. Medicaid Integrity Program: South Carolina comprehensive program integrity review- final report. 2011.

64. West Virginia Medicaid. West Virgina Medicaid Lock-In Program: Outcomes Assessment. 2013.

65. Fleming DK, Homar R, Oleske I, Sherard B, Melinkovich G. Prescription drug cost containment report. 2004.

66. Beaubien JM. Effectiveness of recipient restriction programs in Medicaid managed care organizations. *University of Rhode Island [Dissertation].* 2005.

67. Dreyer TR, Michalski T, Williams BC. Patient Outcomes in a Medicaid Managed Care Lock-In Program. *Journal of Managed Care & Specialty Pharmacy.* 2015;21(11):1006-1012.

68. Association for Community Affiliated Plans. Strategies to reduce prescription drug abuse: lessons learned from the ACAP SUD collaborative. 2015.

69. NC Division of Medical Assistance- Pharmacy and Ancillary Services. Curbing prescription drug abuse in Medicaid. 2010.

70. Targeted News Service. Medicaid narcotics 'lock-in' program saves money, improves care. *Press Release, Gov Beverly Perdue.* 2011.

71. Deen B. 2.3 million pills off the streets, $5.2 million saved by narcotics lockin. 2012.

72. Mitchell L. Lock-in program promotes appropriate use of resources. *The Journal of the Oklahoma State Medical Association.* 2009;102(8):276.

73. Tanenbaum S, Dyer J. The dynamics of prescription drug abuse and its correctives in one state Medicaid program. 1990.

74.   Skinner AC. CDC Grant #U01 CE002160-01: Change in opioid use and overdose after a medicaid lock-in program. 2012.

75.   National Alliance for Model State Drug Laws. Prescription drug abuse, addiction, and diversion: Overview of state legislative and policy initiatives, Part 1. 2014.

76.   Skinner AC, Sachdeva N, Moss L, et al. Reducing opioid misuse: evaluation of a Medicaid lock-in program. *AcademyHealth's Annual Research Meeting (poster presentation).* 2015.

77.   Skinner AC, Roberts AW, Sachdeva N, et al. Obtaining opioids through circumvention of the Medicaid program: effect of a narcotic lock-in program. *AcademyHealth's Annual Research Meeting (poster presentation).* 2015.

78.   Roberts AW, Farley J, Holmes M, Oramasionwu CU, Sleath B, Skinner AC. Minding the lock-in: a longitudinal analysis of patient-level predictors of circumvention in a Medicaid controlled substance lock-in program. *AcademyHealth's Annual Research Meeting (poster presentation).* 2015.

79.   Roberts AW. Optimizing the public health benefit of a Medicaid controlled substance lock-in program. *University of North Carolina [Dissertation].* 2015.

80.   Skinner AC, Ringwalt C, Naumann RB, et al. Reducing Opioid Misuse: Evaluation of a Medicaid Controlled Substance Lock-In Program. *The Journal of Pain.* 2016;17(11):1150-1155.

81.   Skinner AC. Reducing opioid misuse: the North Carolina Medicaid lock-in program. *Health Policy Class Presentation.* 2015.

82.   Werth RA SN, Roberts AW, Garrettson M, Ringwalt C, Moss LA, Pikoulas T, Skinner AC. . North Carolina Medicaid Recipient Management Lock-In Program: The Pharmacist's Perspective. *Journal of Managed Care Pharmacy.* 2014;20(10).

83.   Roberts AW, Farley JF, Holmes GM, et al. Controlled Substance Lock-In Programs: Examining An Unintended Consequence Of A Prescription Drug Abuse Policy. *Health Affairs.* 2016;35(10):1884-1892.

84.   Wu LT, Woody GE, Yang C, Blazer DG. Subtypes of nonmedical opioid users: results from the national epidemiologic survey on alcohol and related conditions. *Drug & Alcohol Dependence.* 2010;112(1-2):69-80.

85.   Liu LC, Hedeker D, Segawa E, Flay BR. Evaluation of Longitudinal Intervention Effects: An Example of Latent Growth Mixture Models for Ordinal Drug-Use Outcomes. *Journal of Drug Issues.* 2010;40(1):27-43.

86.   Yeh HH, Chen CY, Fang SY, Chang IS, Wu EC, Lin KM. Five-year trajectories of long-term benzodiazepine use by adolescents: patient, provider, and medication factors. *Psychiatric Services.* 2011;62(8):900-907.

87. Kertesz SG, Khodneva Y, Richman J, et al. Trajectories of drug use and mortality outcomes among adults followed over 18 years. *Journal of General Internal Medicine.* 2012;27(7):808-816.

88. Huang D, Brecht ML, Hara M, Hser YI. Influences of a Covariate on Growth Mixture Modeling. *Journal of Drug Issues.* 2010;40(1):173-194.

89. Nosyk B, Guh DP, Sun H, et al. Health related quality of life trajectories of patients in opioid substitution treatment. *Drug & Alcohol Dependence.* 2011;118(2):259-264.

90. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. *Drug & Alcohol Dependence.* 2009;104(1-2):34-42.

91. Green TC, Black R, Grimes Serrano JM, Budman SH, Butler SF. Typologies of prescription opioid use in a large sample of adults assessed for substance abuse treatment. *PloS One.* 2011;6(11):e27244.

92. Jones B. Proc Traj: A SAS procedure for group based modeling of longitudinal data. 2007.

93. Jones B, Nagin, DS, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. *Sociological Methods & Research.* 2001;29(3):374-393.

94. Jung T WA. An introduction to latent class growth analysis and growth mixture modeling. *Social and Personality Psychology Compass.* 2008;2(1):302-317.

95. Nagin DS, Odgers CL. Group-Based Trajectory Modeling (Nearly) Two Decades Later. *Journal of Quantitative Criminology.* 2010;26(4):445-453.

96. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annual Review of Clinical Psychology.* 2010;6:109-138.

97. Nagin DS. *Group-based Modeling of Development*. 2005.

98. Nagin DS. Analyzing developmental trajectories: a semi-parametric, group-based approach. *Psychological Methods.* 1999;4(2):139-177.

99. Jackson KM, Sher KJ. Similarities and differences of longitudinal phenotypes across alternate indices of alcohol involvement: a methodologic comparison of trajectory approaches. *Psychology of Addictive Behaviors.* 2005;19(4):339-351.

100. Reinecke J. Longitudinal analysis of adolescents' deviant and delinquent behavior: Applications of latent class growth curves and growth mixture models. *Methodology.* 2006;2:100-112.

101. North Carolina State Legislature. North Carolina Controlled Substances Reporting System Act, NCGS 90-113.70. 2005.

102.   Garrettson M, Ringwalt C. An evaluation of the North Carolina Controlled Substances Reporting System: Part 1 User Surveys. 2013.

103.   North Carolina Department of Health and Human Services. Controlled Substances Reporting System. 2015.

104.   The Henry J. Kaiser Family Foundation. Medicaid in North Carolina Fact Sheet. 2017.

105.   Community Care of North Carolina. The Community Care of North Carolina Toolkit: Creating an Informatics Center and Accountability/Feedback. 2015.

106.   Centers for Medicare and Medicaid Services. Medicaid Management Information Systems (MMIS). 2015.

107.   North Carolina General Assembly- Program Evaluation Division. North Carolina needs to strengthen its system for monitoring and preventing the abuse of prescribed controlled substances. 2014.

108.   Community Care of North Carolina, Project Lazarus. Chronic Pain Initiative Tool Kit: Primary Care Provider. 2012.

109.   Prescription Drug Monitoring Program: Training and Technical Assistance Center. Calculating Daily Morphine Milligram Equivalents: Technical Assistance Guide No.01-13. 2013.

110.   Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort Study of the Impact of High-dose Opioid Analgesics on Overdose Mortality. *Pain Medicine.* 2016;17(1):85-98.

111.   Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Annals of Internal Medicine.* 2010;152(2):85-92.

112.   Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *Journal of the American Medical Association.* 2011;305(13):1315-1321.

113.   Paulozzi LJ, Kilbourne EM, Shah NG, et al. A History of Being Prescribed Controlled Substances and Risk of Drug Overdose Death. *Pain Medicine.* 2012;13(1):87-95.

114.   Centers for Disease Control and Prevention. Centers for Disease Control and Prevention's compilation of opioid analgesic formulations with morphine milligram equivalent conversion factors, 2015 version. 2015.

115.   Centers for Medicare and Medicaid Services. Opioid Morphine Equivalent Conversion Factors. 2015.

116.   Von Korff M, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. *Clinical Journal of Pain.* 2008;24(6):521-527.

117. National Institute on Drug Abuse. Prescription drugs: abuse and addiction. *NIDA Research Report Series.* 2011.

118. Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. 2013.

119. Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System (WISQARS) [online]. 2016.

120. Campbell CI, Weisner C, Leresche L, et al. Age and gender trends in long-term opioid analgesic use for noncancer pain. *American Journal of Public Health.* 2010;100(12):2541-2547.

121. Williams RE, Sampson TJ, Kalilani L, Wurzelmann JI, Janning SW. Epidemiology of opioid pharmacy claims in the United States. *Journal of Opioid Management.* 2008;4(3):145-152.

122. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *Journal of the American Medical Association.* 2008;300(22):2613-2620.

123. Cai R, Crane E, Poneleit K, Paulozzi L. Emergency department visits involving nonmedical use of selected prescription drugs-- United States, 2004-2008. *Morbidity & Mortality Weekly Report (MMWR).* 2010;59(23):705-709.

124. Centers for Disease Control and Prevention. Health, United States, 2006, with Chartbook. 2006.

125. Gu Q, Dillon CF, Burt VL. Prescription drug use continues to increase: U.S. prescription drug data for 2007-2008. *NCHS Data Brief.* 2010;42.

126. North Carolina Department of Health and Human Services. Adult Medicaid Manual. 2016.

127. Young AM, Havens JR, Leukefeld CG. A comparison of rural and urban nonmedical prescription opioid users' lifetime and recent drug use. *The American Journal of Drug and Alcohol Abuse.* 2012;38(3):220-227.

128. Paulozzi LJ, Xi Y. Recent changes in drug poisoning mortality in the United States by urban-rural status and by drug type. *Pharmacoepidemiology and Drug Safety.* 2008;17(10):997-1005.

129. Cicero TJ, Surratt H, Inciardi JA, Munoz A. Relationship between therapeutic use and abuse of opioid analgesics in rural, suburban, and urban locations in the United States. *Pharmacoepidemiology and Drug Safety.* 2007;16(8):827-840.

130. Modarai F, Mack K, Hicks P, et al. Relationship of opioid prescription sales and overdoses, North Carolina. *Drug & Alcohol Dependence.* 2013;132(1-2):81-86.

131. U.S. Department of Agriculture Economic Research Service. Rural-Urban Continuum Codes, 2013 update. 2016.

132. North Carolina Department of Health and Human Services. County-Level Poisoning Data. 2017.

133. Albert S, Brason FW, 2nd, Sanford CK, Dasgupta N, Graham J, Lovette B. Project Lazarus: community-based overdose prevention in rural North Carolina. *Pain Medicine.* 2011;12 Suppl 2:S77-85.

134. Becker WC, Sullivan LE, Tetrault JM, Desai RA, Fiellin DA. Non-medical use, abuse and dependence on prescription opioids among U.S. adults: psychiatric, medical and substance use correlates. *Drug & Alcohol Dependence.* 2008;94(1-3):38-47.

135. Edlund MJ, Martin BC, Devries A, Fan M-Y, Braden JB, Sullivan MD. Trends in use of opioids for chronic non-cancer pain among individuals with mental health and substance use disorders: the TROUP study. *The Clinical Journal of Pain.* 2010;26(1):1-8.

136. Edlund MJ, Martin BC, Fan MY, Devries A, Braden JB, Sullivan MD. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: results from the TROUP study. *Drug & Alcohol Dependence.* 2010;112(1-2):90-98.

137. Tetrault JM, Desai RA, Becker WC, Fiellin DA, Concato J, Sullivan LE. Gender and non-medical use of prescription opioids: results from a national US survey. *Addiction.* 2008;103(2):258-268.

138. Edlund MJ, Martin BC, Fan MY, Braden JB, Devries A, Sullivan MD. An analysis of heavy utilizers of opioids for chronic noncancer pain in the TROUP study. *Journal of Pain and Symptom Management.* 2010;40(2):279-289.

139. Agency for Healthcare Research and Quality (AHRQ). Clinical Classification Software for ICD-9-CM. 2016.

140. Stein BD, Gordon AJ, Sorbero M, Dick AW, Schuster J, Farmer C. The impact of buprenorphine on treatment of opioid dependence in a Medicaid population: Recent service utilization trends in the use of buprenorphine and methadone. *Drug & Alcohol Dependence.* 2012;123(1–3):72-78.

141. Mohlman MK, Tanzman B, Finison K, Pinette M, Jones C. Impact of Medication-Assisted Treatment for Opioid Addiction on Medicaid Expenditures and Health Services Utilization Rates in Vermont. *Journal of Substance Abuse Treatment.* 2016;67:9-14.

142. Harmon K, Barnett C, Proescholdbell S, Waller A, Dellapenna A, Marshall S. The North Carolina Surveillance Quality Improvement Project (Year One): An Assessment of the Completeness of External Cause of Injury Coding among North Carolina Acute-care Emergency Departments. 2012.

143. Harmon K, Ising A, Proescholdbell S, Barnett C, Marshall S, Waller A. 0035 Development of 12 poisoning and drug overdose case definitions for use with emergency department data in North Carolina. *Injury Prevention.* 2015;21(Suppl 1):A27-A28.

144. Harmon K, Ising A, Waller A. ICD-9-CM case defintions for poisoning-- NC DETECT emergency department data. *Carolina Center for Health Informatics, Department of Emergency Medicine, University of North Carolina at Chapel Hill and the Injury Prevention Research Center, Univeristy of North Carolina at Chapel Hill.* 2014.

145. Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Trends in use of opioids for non-cancer pain conditions 2000-2005 in commercial and Medicaid insurance plans: the TROUP study. *Pain.* 2008;138(2):440-449.

146. Katz C, El-Gabalawy R, Keyes KM, Martins SS, Sareen J. Risk factors for incident nonmedical prescription opioid use and abuse and dependence: results from a longitudinal nationally representative sample. *Drug & Alcohol Dependence.* 2013;132(1-2):107-113.

147. Edlund MJ, Martin BC, Devries A, Fan MY, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. *The Clinical Journal of Pain.* 2010;26(1):1-8.

148. Novak SP, Herman-Stahl M, Flannery B, Zimmerman M. Physical pain, common psychiatric and substance use disorders, and the non-medical use of prescription analgesics in the United States. *Drug & Alcohol Dependence.* 2009;100(1-2):63-70.

149. Howe CQ, Sullivan MD. The missing 'P' in pain management: how the current opioid epidemic highlights the need for psychiatric services in chronic pain care. *General Hospital Psychiatry.* 2014;36(1):99-104.

150. Martins SS, Fenton MC, Keyes KM, Blanco C, Zhu H, Storr CL. Mood and anxiety disorders and their association with non-medical prescription opioid use and prescription opioid-use disorder: longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions. *Psychological Medicine.* 2012;42(6):1261-1272.

151. Toblin RL, Paulozzi LJ, Logan JE, Hall AJ, Kaplan JA. Mental illness and psychotropic drug use among prescription drug overdose deaths: a medical examiner chart review. *The Journal of Clinical Psychiatry.* 2010;71(4):491-496.

152. Thielke SM, Simoni-Wastila L, Edlund MJ, et al. Age and sex trends in long-term opioid use in two large American health systems between 2000 and 2005. *Pain Medicine.* 2010;11(2):248-256.

153. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases.* 1987;40(5):373-383.

154. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care.* 2005;43(11):1130-1139.

155. Merrill JO, Von Korff M, Banta-Green CJ, et al. Prescribed opioid difficulties, depression and opioid dose among chronic opioid therapy patients. *General Hospital Psychiatry.* 2012;34(6):581-587.

156. Gokhale M, Girman C, Chen Y, Pate V, Funk MJ, Sturmer T. Comparison of diagnostic evaluations for cough among initiators of angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Pharmacoepidemiology and Drug Safety.* 2016.

157. Brookhart MA, Stürmer T, Glynn RJ, Rassen J, Schneeweiss S. Confounding control in healthcare database research: challenges and potential approaches. *Medical Care.* 2010;48(6 0):S114-S120.

158. Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *American Journal of Epidemiology.* 2001;154(9):854-864.

159. Ram N, Grimm KJ. Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups. *International Journal of Behavioral Development.* 2009;33(6):565-576.

160. Bauer DJ, Curran PJ. Latent curve modeling. Chapel Hill, NC: Curran-Bauer Analytics Course. 2015.

161. Nagin DS. Group-based trajectory modeling: an overview. *Annals of Nutrition & Metabolism.* 2014;65(2-3):205-210.

162. Academy of Managed Care Pharmacy. Comprehensive Addiction and Recovery Act of 2016 Public Law: 114-198. 2016.

163. Blue Cross Blue Shield. The Blue Cross and Blue Shield System's Commitment to Fighting Opioid Addiction and Deaths 2016.

164. Anthem. New pharmacy home program helps high-risk members. 2016.

165. Roberts AW, Gellad WF, Skinner AC. Lock-In Programs and the Opioid Epidemic: A Call for Evidence. *American Journal of Public Health.* 2016;106(11):1918-1919.

166. Stein BD, Gordon AJ, Sorbero M, Dick AW, Schuster J, Farmer C. The impact of buprenorphine on treatment of opioid dependence in a Medicaid population: recent service utilization trends in the use of buprenorphine and methadone. *Drug & Alcohol Dependence.* 2012;123(1-3):72-78.

167. North Carolina Department of Health and Human Services, Division of Public Health. Proposed Public Health Surveillance Definitions for Poisoning and Overdose. 2015.

168. Yang D, Dalton JE. A unified approach to measuring the effect size between two groups using SAS. *SAS Global Forum.* 2012;Paper 335-2012.

169. Brunelli SM, Gagne JJ, Huybrechts KF, et al. Estimation Using All Available Covariate Information Versus a Fixed Look-back Window for Dichotomous Covariates. *Pharmacoepidemiology and Drug Safety.* 2013;22(5):10.1002/pds.3434.

170. Centers for Medicare and Medicaid Services. Chronic conditions data warehouse. 2016.

171. Reeves S, Garcia E, Kleyn M, et al. Identifying sickle cell disease cases using administrative claims. *Academic Pediatrics.* 2014;14(5 Suppl):S61-67.

172. Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. *American Journal of Public Health.* 2009;99(2):221-227.

173. North Carolina Medicaid. Implementation of a recipient management lock-in program. *North Carolina Medicaid Pharmacy Newsletter.* 2010.

174. Naumann RB, Marshall SM, Lund JL, Skinner AC, Ringwalt C, Gottfredson NC. Attributes of Medicaid beneficiaries eligible, enrolled, and retained in a controlled substance "lock-in" program. 2017:Under review.

175. Naumann RB, et al. Evaluating short- and long-term impacts of a Medicaid "lock-in" program on controlled substances dispensed to beneficiaries. 2017:Under review.

176. Lopez-Castro T, Hu MC, Papini S, Ruglass LM, Hien DA. Pathways to change: Use trajectories following trauma-informed treatment of women with co-occurring post-traumatic stress disorder and substance use disorders. *Drug and Alcohol Review.* 2015;34(3):242-251.

177. Sterba SK, Bauer DJ. Predictions of Individual Change Recovered With Latent Class or Random Coefficient Growth Models. *Structural Equation Modeling-a Multidisciplinary Journal.* 2014;21(3):342-360.

178. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain-- United States, 2016. *Morbidity & Mortality Weekly Report (MMWR).* 2016;ePub: 15 March 2016.

179. Bauer DJ. Observations on the use of growth mixture models in psychological research. *Multivariate Behavioral Research.* 2007;42:757-786.

180. Bauer DJ, Curran PJ. The integration of continuous and discrete latent variable models: potential problems and promising opportunities. *Psychological Methods.* 2004;9(1):3.

181. Centers for Disease Control and Prevention. Integrating & Expanding Prescription Drug Monitoring Program Data: Lessons from Nine States. 2017.

182. Katz N, Panas L, Kim M, et al. Usefulness of prescription monitoring programs for surveillance--analysis of Schedule II opioid prescription data in Massachusetts, 1996-2006. *Pharmacoepidemiology and Drug Safety.* 2010;19(2):115-123.

183. Ohio Department of Health. Ohio drug poisoning fact sheet: epidemic of prescription drug overdoses in Ohio. 2012.

184. Lanier W. Prescription opioid overdose deaths-- Utah, 2008-2009. *59th Annual Epidemic Intelligence Conference.* 2010;April 19-23, 2010.

185. Paulozzi L, Baldwin G, Franklin G, et al. CDC Grand Rounds: Prescription Drug Overdoses-- a U.S. Epidemic. *Morbidity & Mortality Weekly Report (MMWR).* 2012;61(01):10-13.

186. American Society of Addiction Medicine. Public Policy Statement on Patient Review and Restriction (PRR) Programs. 2016.

187. Hipp JR, Bauer DJ. Local solutions in the estimation of growth mixture models. *Psychological Methods.* 2006;11(1):36-53.

188. Lo Y, Mendell NR, Rubin DB. Testing the number of components in a normal mixture. *Biometrika.* 2001;88(3):767-778.

189. Berlin KS, Williams NA, Parra GR. An introduction to latent variable mixture modeling (part 1): overview and cross-sectional latent class and latent profile analyses. *Journal of Pediatric Psychology.* 2014;39(2):174-187.

190. Clark SL, Muthén B. Relating latent class analysis results to variables not included in the analysis. *MPlus Resources.* 2009;Available from: https://www.statmodel.com/download/relatinglca.pdf.

191. Petras H, Masyn K. General Growth Mixture Analysis with Antecedents and Consequences of Change. In: Piquero AR, Weisburd D, eds. *Handbook of Quantitative Criminology*. New York, NY: Springer New York; 2010:69-100.

192. Bolck A, Croon M, Hagenaars J. Estimating Latent Structure Models with Categorical Variables: One-Step Versus Three-Step Estimators. *Political Analysis.* 2004;12(1):3-27.

193. Vermunt JK. Latent Class Modeling with Covariates: Two Improved Three-Step Approaches. *Political Analysis.* 2010;18(4):450-469.