EVALUATION OF MEDICAL EXPENDITURE ASSOCIATED WITH OPIOID USAGE IN CHRONIC NON-CANCER PAIN

A Dissertation

by

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ABSTRACT

In the United States, as of 2016 there were around 28 million individuals with chronic non-cancer pain (CNCP) conditions. If uncontrolled, CNCP can have enormous economic, societal and health consequences. Currently, a common treatment for CNCP is long-term opioid therapy. If used properly, opioid treatment can relieve pain and increase quality of life with manageable adverse effects. However, opioid treatment is controversial due to the health and economic burden from the potential for addiction and other serious adverse effects, and from the prevalence of diversion of opioids to non-therapeutic uses. This retrospective study estimates the impact of pain management with and without opioids on medical expenditures for CNCP conditions. The data sources are 12-years Medical Expenditure Panel Survey (MEPS) data and 5-years commercial claims data from Blue Cross Blue Shield of Texas (BCBSTX). Two analytic approaches were applied to both data sets: 1) cross-sectional descriptive analysis and regression models to evaluate differences in service utilization and expenditure among CNCP patients with and without opioid treatment; and 2) longitudinal analysis to examine changes in health outcomes and expenditures for before and after new episodes of opioid treatment for CNCP patients. Results from analyses of both datasets indicated higher CNCP treatment costs associated with opioid treatment.

DEDICATION

I dedicate my dissertation work to my family. I have a special feeling of gratitude to my loving parents, Xiaoning Zhang and Xinxin Lyu whose words of encouragement and push for tenacity ring in my ears.

This work is dedicated to my son Ethan. You have made me stronger, better and more fulfilled than I could have ever imagined.

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This work was supervised by a dissertation committee consisting of Professor Robert L. Ohsfeldt, Professor Tiffany A. Radcliff, and Professor Murray J. Côté of the Department of Health Policy and Management Department, and Professor Hongwei Zhao of the Department of Biostatistics, as well as Professor Ellerie Weber from the Department of Management, Policy & Community Health at the University of Texas Health Science Center School of Public Health.

Part 2, student/collaborator contributions

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NOMENCLATURE

CNCP	Chronic Non-Cancer Pain
WHO	World Health Organization
OIH	Opioid-Induced Hyperalgesia
MEPS	Medical Expenditure Panel Survey
AHRQ	Agency for Healthcare Research and Quality
ICD	International Statistical Classification of Diseases and Related Health Problems
HC	Household Component
MPC	Medical Provider Component
NDC	National Drug Code
PS	Propensity Score
GLM	Generalized Linear Model
GLMMs	Generalized Linear Mixed Models
OLS	Ordinary Linear Regression
SES	Social Economics Status
SD	Standard Deviation
SE	Standard Error
CPI	Consumer Price Index
BCBS	Blue Cross Blue Shield
TX	Texas

FE	Fixed Effect
RE	Random Effect

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CHAPTER 1. INTRODUCTION

According to a well-cited report from the Institute of Medicine (IOM) "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research," there are 100 million Americans suffering from chronic pain (IOM, 2011; Simon, 2012), with an associated cost of $560 to $635 billion annually in lost productivity and medical care (Gaskin & Richard, 2012). Among all chronic pain patients, there were around 28 million individuals with chronic non-cancer pain (CNCP) conditions (Chou, Fanciullo, Fine, Adler, et al., 2009).

If uncontrolled, CNCP can have enormous economic, societal and health consequences. A 2015 study estimated the annual consumption of healthcare resources among patients suffering from CNCP are nearly twice the level of the consumption of healthcare resources in the general population (Henschke, Kamper, & Maher, 2015). Currently, a common treatment for CNCP is long-term opioid therapy, which is controversial due to the need to balance the benefits to patients of more effective pain management with the risk for addiction and abuse.

From 2000 to 2010, the prevalence of individuals diagnosed with conditions indicative of chronic pain has been consistent, but over the same period the rate of opioid prescriptions among patients with chronic pain conditions almost doubled, from 11.3% to 19.6% (Daubresse et al., 2013). Although by 2017 the volume of total opioid prescriptions had declined 29% from the peak volume in 2011 (IQVIA, 2018), American Society of Addiction Medicine estimated 20,101 overdose deaths related to prescription

pain relievers in 2016. (American Society of Addiction Medicine, 2016). On October 27th, 2017, the Trump administration declared the opioid crisis a public health emergency.

Many previous studies have investigated CNCP and opioid use from different perspectives to investigate the medical and social impact of CNCP conditions, and the cost and outcomes of opioid treatment on CNCP population (Campbell et al., 2015; Henschke et al., 2015; Kern et al., 2015; Vowles et al., 2015). Some studies estimated the economic burden of opioid treatment by secondary data analysis or clinical trials, and tried to prove higher healthcare utilization for long term opioid treatment to CNCP (Kirson et al., 2017; Kay, Wozniak, & Bernstein, 2017; Scarpati, Kirson, Jia, Wen, & Howard, 2017).

Still, little had been known about the impact of opioid treatment on healthcare costs for CNCP patients overtime, and the specific treatments constituting the major drivers of cost differences. Other longitudinal studies have described the pattern of healthcare utilization and cost over a long term (more than 1 year) adjusted for patients' characteristics, treatment pattern, and other related factors (Kern et al., 2015; Maeng, Han, Fitzpatrick, & Boscarino, 2017). But the studies were based on claims data from a solo healthcare system, lacking the generalization to represent the national scale, not to mention these two studies included all types of chronic patients and did not focus on CNCP patients.

The objective of this study is to estimate medical expenditures and utilization patterns for CNCP patients using a longitudinal national sample obtained from several

years of Medical Expenditure Panel Survey (MEPS) data and replicate the MEPS results using commercial claims data from Blue Cross Blue Shield of Texas (BCBSTX). The specific aims of the study include: 1) cross-sectional analysis to estimate annual total medical expenditure for CNCP patients with and without opioid treatment, and 2) longitudinal analysis to estimate the difference in medical expenditure for CNCP patients initiation or not new opioid treatment episode.

1.1 Literature Review

In this section, I reported the results of a comprehensive literature review to explore the definition, pathogenesis, effectiveness of treatments, and economic impact of CNCP and opioid treatment for CNCP patients. The review was divided into three parts: 1) Definition, Prevalence, and Management for CNCP; 2) Effectiveness and Side-effects of Opioid Treatments for CNCP; and 3) Medical Expenditures and Economics Burden of Opioid Treatment for CNCP.

1.1.1 Definition, Prevalence, and Management for CNCP

The International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (IASP, 1994). The American Pain Society defined chronic or long-term pain as pain sustained more than six months, which disturbs numerous lives all over the world across different ages and genders (The American Pain Society, 2000).

Due to the variances of pathophysiological mechanisms, chronic pain often was classified as chronic cancer pain or chronic non-cancer pain (CNCP) (Dennis C. Turk & Okifuji, 1998). The term chronic non-cancer pain (CNCP) relates to many kinds of conditions, including musculoskeletal pain, neuropathic pain, fibromyalgia, osteoarthritis and rheumatoid arthritis, but excluding headache, migraine, angina pectoris, cancer pain and pain associated with specific disease conditions (e.g. multiple sclerosis) (Reid, et al., 2011).

In the United States, the Institute of Medicine estimated that there were around 116 million Americans with chronic pain conditions (Committee on Advancing Pain Research Care & Institute of Medicine, 2011), of which 78% are CNCP (Croft, 2010). A more conservative estimate by the Mayday Fund assessed the prevalence of chronic pain is 70 million Americans (Mayday Fund, 2009). In 15 European countries and Israel, one large-scale computer-assisted telephone survey revealed that 19% of the participants had suffered chronic pain, 34% of those affected by chronic pain had severe pain and 60% visited their doctor due to their pain 2-9 times during the last six months (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006).

According to the American Pain Society, in 2010, 25% of the adult population had moderate to severe CNCP, which was disabling for 10% of the population (Croft, 2010), and 6% of the adult population have had pain for more than 5 years, which significantly reduced their quality of life (The American Pain Society, 2000).

According to the IOM, the prevalence of CNCP was expected to continue to grow (Institute of Medicine, 2011). Several factors contributed to this expected growth.

Lifespans for general population had been increasing, and the baby-boom generation had been getting older. Population aging was increasing the prevalence of chronic conditions associated with chronic pain (Lipton, 2011). Moreover, advances in trauma medicine had reduced the rate of mortality from severe traumatic accidents, but survivors often have chronic pain conditions. Also, the obesity epidemic was becoming a serious health and social problem in the United States. Studies indicated that obesity increased the risk of chronic pain through a pro-inflammatory condition, which contributed to the growth in aggregate CNCP prevalence (McCarthy, Bigal, Katz, Derby, & Lipton, 2009).

CNCP is not only one of the most prevalent reasons for doctor visits, but also reduces people's quality of life (Gureje, Von Korff, Simon, & Gater, 1998). The Collaborative Study of Psychological Problems in General Health Care, which was conducted by the World Health Organization (WHO), predicted that 22% of primary care patients had pain persisting more than five months that restricted their daily activities and requires medical care (Gureje et al., 1998; Sullivan et al., 2008). Undoubtedly, CNCP conditions are serious health problems with heavy cost implications. One study estimated the general economic costs for CNCP was around $560 to $635 billion per year (in 2010-dollars) (Gaskin & Richard, 2012).

If not managed properly, CNCP could cause complicated and serious health outcomes for patients. It interferes with patients' daily activities, disrupts sleep, decreases the productivity for their work, affects mood and might cause mental health problems. The risk of suicide for CNCP patients was almost twice the risk for individuals without chronic pain (Chapman, 2013).

The growth in the prevalence of CNCP, often coupled with the inadequate management of chronic pain, creating a dilemma for opioid treatment. Since cancer pain is predominantly somatogenic, the prevailing treatments for cancer pain are "with pharmacological, medical, or surgical modalities" (Dennis C. Turk et al., 1998). To be more specific, the treatments could include epidural, intrathecal anaesthetic or spinal anaesthetic, as well as coeliac plexus, splanchnicectomy or thoracoscopic sympathectomy (nerve block), plus electrical nerve stimulation (TENS) and acupuncture and so on (National Institute on Drug Abuse, 2018).

Otherwise, in the absence of adequate objective physical pathology and limited understandings of nociceptive or neuropathic nature (Dennis C. Turk et al., 1998), some CNCP conditions had been caused, increased, or prolonged by mental, emotional, or behavioral factors (Lian, Shah, Mueller, & Welliver, 2017), such as headache, back pain, or stomach pain (Cheng, 2018). These sources of pain often are regarded as psychogenic pain with no objectively observed cause, but in most cases CNCP is associated with organic processes that exacerbate pain noticeably (Chandler, Dinterstein, Haythornthwaite, & Wager, 2015). The treatment for psychogenic pain is harder than nociceptive pain or neuropathic pain, since the traditional treatments are designed for inflammation or nerve dysfunction conditions (Portenoy et al., 2007). Opioid treatment is especially inappropriate for psychogenic pain (A. Rosenblum, Marsch, Joseph, & Portenoy, 2008).

Past studies suggest CNCP were managed most effectively using a multidisciplinary approach, which included psychological interventions, physical

therapies, and nutrition treatment (Jeffery, Butler, Stark, & Kane, 2011; Scascighini, Toma, Dober-Spielmann, & Sprott, 2008, Dennis C. Turk, Wilson, & Cahana, 2013; Health Quality, 2016; Perry, VanDenKerkhof, Wilson, & Tripp, 2017). However, various reasons made multidisciplinary treatment less appealing in reality, such as lack of certified pain specialists, physicians who are not well-prepared to manage CNCP, and difficulty in coordinating the multidisciplinary treatment by different providers, as well as resistance from payers (Chapman, 2013; Perry et al., 2017). Though its long-term efficacy has been questioned (Rosenblum et al., 2003), opioids are commonly used as a long-term treatment for CNCP. Opioids work by exerting their activity on opioid receptors, and have been considered as "the most potent analgesics for the treatment of severe acute, surgical and cancer pain" (Furlan, Sandoval, Mailis-Gagnon, & Tunks, 2006; Heit, 2001). Boudreau et al. (Boudreau et al., 2009) estimate that more than 3% of adults with CNCP condition received chronic opioid therapy.

In the last twenty years, there has been a growing trend of using opioid treatments for CNCP. Although opioids treatments have been used for acute pain for a long time, the cost-effectiveness of opioids for CNCP is still controversial. Before the 1990s, opioids were mainly used for patients with advanced cancer. However, in 1986, a retrospective study of 38 CNCP patients with long-term opioid treatment showed success of pain relief without significant adverse effect (Portenoy & Foley, 1986). Followed by many studies with similarly positive results, Portenoy and Foley's study changed the landscape of the CNCP treatment.

The pharmaceutical industry seized this chance to develop new opioid drugs and to market them aggressively by developing patient advocacy and physician education programs. The new drug got FDA approval during 90s included Duragesic in 1990, OxyContin in 1995, and Actiq (fentanyl) in 1998 (FDA, 2018). OxyContin is the first formulation of oxycodone which can be dosed every 12 hours rather than 4 to 6 hours and the controlled-release capsule design caused unexpected high level of abuse by oral ingestion or snorting. Back to then, FDA believed the controlled-release formulation of OxyContin could reduce potential abuse due to the slow absorbing of the drug to avoid the immediate high that causes abuse. In 1997, a consensus statement was published jointly by the American Pain Society and the American Academy of Pain Medicine provided guidelines which endorsed the use of opioid treatment for CNCP. The guideline said, "Opioid are an essential part of a pain management part" (American Academy of Pain Medicine & American Pain Society, 1997).

From 2000 to 2010, the diagnosis of primary symptoms of pain has been consistent, but opioid prescriptions increased almost two-fold from 11.3% to 19.6% (Daubresse et al., 2013). While by 2017 the volume of total opioid prescriptions had declined 29% from the peak volume in 2011 (IQVIA, 2018), the Center for Behavior Health Statistics and Quality estimated there 10,635,000 adults that misused pain relievers in year 2016 (Substance Abuse and Mental Health Services Administration, 2017). Coupled with the increase of consumption of opioids for CNCP, the painkiller overdoses related emergency department visits and mortality ratio have increased (Braden, Russo, Fan, & et al., 2010; Dart et al., 2015). American Society of Addiction

Medicine estimates 20,101 overdose deaths related to prescription pain relievers in 2016 (American Society of Addiction Medicine, 2016).

1.1.2 Effectiveness and adverse-effects of opioid treatments

The major concerns about long-term opioid treatment for CNCP include the unclear effectiveness and adverse-effects of opioids, the physical tolerance due to usage of opioids, addiction and abuse of opioids (Furlan et al., 2006). Some researchers argued that although the usage and abuse of therapeutic opioids increased dramatically during the past 15 to 20 years, there still is not clear evidence for "the effectiveness of opioids for chronic non-cancer pain" (Manchikanti, Fellows, & Ailinani, 2010). Other studies also conclude that strong evidence supporting the effectiveness of opioids for the treatment of CNCP is lacking (Chou, Fanciullo, Fine, Miaskowski, et al., 2009; Manchikanti et al., 2010; Manchikanti & Singh, 2008; Trescot et al., 2008).

Beyond concerns about the efficacy for therapeutic opioids usage for CNCP, other studies have raised concerns about various adverse effects of opioid treatment. These included "problematic physiologic effects" such as "hyperalgesia (Abs et al., 2000), hypogonadism and sexual dysfunction" (Angst & Clark, 2006), and adverse side effects that the potential for misuse and abuse and the increase in opioid-related deaths (Robinson et al., 2001). In a serial cross-sectional analysis, Gomes et al found that the percentage of all deaths attributable to opioids increased 292% (from 0.4% to 1.5%) between 2001 and 2016, resulting in approximately 1.68 million person-years of life lost in 2016 alone (5.2 per 1000 population). The burden was particularly high among adults aged 24 to 35 years; in 2016, 20% of deaths in this age group involved opioids (Gomes,

Tadrous, Mamdani, Paterson, & Juurlink, 2018). Some studies tried to investigate the factors contributing to increase of opioid prescription and the correlation ship to the overdose death. Hadland et al. found marketing of opioid products to physicians was associated with increased opioid prescribing and, subsequently, with raised mortality from overdoses. Addressing a national opioid overdose crisis, it is necessary to explore the influence of the pharmaceutical industry (Hadland, Rivera-Aguirre, Marshall, & Cerdá, 2019).

In order to fully evaluate the impact of opioid treatment, Manchikanti and his colleagues conducted a comprehensive review of literature on the effectiveness of long-term opioid therapy for CNCP. Their primary outcome measure was pain relief and sub-outcome variables included functional improvement and adverse effects (Laxmaiah Manchikanti & Vallejo, 2011). They found that only one specific drug of opioid, tramadol, showed effectiveness of pain relief and improvement of functional status. Due to lack of evidence of effectiveness of long-term opioid therapy for CNCP from the comprehensive review, they claimed more restraint and caution for opioid usage (Laxmaiah Manchikanti & Vallejo, 2011).

Kissin (2013) conducted a scientometic analysis, which was the science of measuring the impact of scientific publications (Harnad, 2009) testing the efficacy of long-term opioid treatment of chronic nonmalignant pain. This study did not discover any randomized controlled trial having opioid treatment for more than three months. Some trials had long-term (longer than 6 months) opioid treatment, but none of them had a control group (Kissin, 2013). This paper reflected the truth of missing consistent high-

quality evidence to support clinical recommendation of long-term opioid treatment (Kissin, 2013).

A more recent systematic review for the effectiveness and risk of long-term opioid therapy for chronic pain found there were no previous studies comparing long-term outcomes of opioid therapy compared to no opioid therapy (Chou et al., 2015). They found there were associations between opioid therapy for chronic pain and the higher chance of overdose, opioid abuse, fractures and some other side effects (Chou et al., 2015). They concluded that there was insufficient evidence to support the effectiveness of long-term opioid treatment for improving chronic pain and function, and limited evidence for association between different doses of opioids. They also investigated the harms related of opioid therapy for chronic pain. They found evidence to show that opioid therapy for chronic pain increased risk for opioid abuse and overdose, fractures, myocardial infarction and utilization of sexual dysfunction medications (Chou et al., 2015). Another review article summarized the existing basic and clinical studies of opioid-induced hyperalgesia (OIH), which is a state of nociceptive sensitization triggered by exposure to opioids (Lee, Silverman, Hansen, Patel, & Manchikanti, 2011). The researchers uncovered that OIH was statistically significant related to the opioid therapy (Angst & Clark, 2006), since for the patients who had long-term opioid treatment, 1) they tended to have greater levels of pain after stopping the long-term opioid treatment; 2) they displayed more sensitive pain response, even to some small procedures; 3) instead of improvement, the long-term opioid treatment aggravated the chronic pain for those patients (Angst & Clark, 2006).

In 2018, Busse et al (Busse et al., 2018) conducted a random-effects meta-analysis to examine the harms and benefits of opioid for CNCP. They reviewed 96 randomized clinical trials with total 26,169 patients with CNCP. The main finds were the opioid treatment reduced CNCP by modest 0.69 cm more than placebo. However, there were several problems of this study: 1) the variability among those studies were high, 2) the random-effects model did not address heterogeneity, 3) the study compared the opioid with placebo, which did not give information about the comparative effectiveness of opioid treatment to other alternative treatments. Overall, considering the amount of heterogeneity, the benefits of opioid treatment would be less or greater than this estimation, depending on the settings and patients. This finding should be used carefully.

Overall, there are few evidence-based studies to show the effectiveness of long-term opioid treatment for CNCP patients. Some clinical trials showed opioid medications were effective for certain CNCP patient populations for a limited time, but these trials lacked a comparison group. There have been no comprehensive studies to distinguish which target specific patient populations could benefit most of be most susceptible to harm by long-term opioid treatment. Plus, these studies used pain rating scales as the primary outcome variables, which neglected the important goal of CNCP management, such as changes of quality of life, restoring work ability, reducing health care expenditures and unnecessary health care utilization, and improved mental status.

Evidence for the efficacy of long-term opioid treatment for CNCP is lacking, but studies have shown evidence for many adverse-effects, such as addiction, opioid-induced dry mouth, nausea, and constipation (Moore & McQuay, 2005), a higher risk of

osteoporosis and bone fracture (A Elliott, E Opper, Agarwal, & E Fibuch, 2012), an increased likelihood of diabetes (Merza, 2010), cardiac complication (Andrews et al., 2009), immunosuppression (Brack, Rittner, & Stein, 2011), and hyperalgesia (Marion Lee, Sanford Silverman, Hans Hansen, & Vikram Patel, 2011). A recent study estimated the rates of adverse events among Veterans Health Administration patients who were using opioid and/or anti-inflammatory drugs found that opioid patients (who used at least 1 opioid between fiscal year 2011 to 2015) had a higher risk of cardiovascular events, acute kidney injury, gastrointestinal bleeding, and all-cause mortality than anti-inflammatory drug users (Fassio, et al., 2018).

Another adverse-effect that has been observed is depression among chronic opioid therapy recipients. Grattan et al. conducted a phone survey of 1,334 patients on chronic opioid therapy for CNCP. The researchers found that in patients without a history of substance abuse, there was a significant association between depressive symptoms and increased rates of self-reported opioid misuse (Grattan, Sullivan, Saunders, Campbell, & Von Korff, 2012). However, the measures of opioid misuse in the study were not sufficient extensive and internally consistent to distinguish the opioid-related misuse from non-pain-symptom-related misuse, such as insomnia and pressure of productivity loss due to the pain (Grattan et al., 2012).

Also, different modes of administration of opioids could lead to several side-effects. The common routes of opioid administration include oral route, enteral tubes, transdermal route, transdermal route, transmucosal, and aerosol (Hallenbeck, 2003). The oral route is the most preferred route, which is cheaper and easy to access, but it takes

hours for short-acting oral agents to reach peak effect and the delayed effect could lead to additional doses. The stacking of multiple doses could lead to overdoes (Hallenbeck, 2003). Compared to the oral route, the enteral tubes can overcome the disadvantage of patients' inability to swallow, except that the enteral tubes cannot release a long-acting agent (Hallenbeck, 2003). The other administration routes are relatively expensive and less used, such as transdermal route, transdermal route, transmucosal, and aerosol (Hallenbeck, 2003). Another administration route of opioid is injection. One European study investigated the effects of administration of opioids via injection into in the space under the arachnoid membrane of the brain or spinal cord on hypothalamic-pituitary function during the pain treatment (Food and Drug Administration, 2011). Among 79 patients, who received opioids for CNCP using this mode of administration, the majority of men and all women developed hypogonadotropic hypogonadism (Abs et al., 2000).

In conjunction with the boost of opioid prescriptions for CNCP treatment in the past 2 decades, there has been increase of opioid abuse and misuse, addiction, and overdose deaths (Kaye et al., 2017). Some researchers estimated opioid abuse in the U. S. population, which was present in 6.7 to 8 per 10,000 insured population and 2.1% of persons aged 12 or older in 2007 (Substance Abuse and Mental Health Services Administration, 2009). Based on community practice surveys, Korff et al. estimated the overall opioid misuse rate is around 4% to 26% (Von Korff, Kolodny, Deyo, & Chou, 2011). Cepeda et al. have done a study with over 25 million patients during 18-months and found 0.3% patients exposed to opioid showing doctor shopping behavior (M. S. Cepeda et al., 2013; M Soledad Cepeda, Fife, Chow, Mastrogiovanni, & Henderson,

2012). Fishbain et al. reviewed 67 studies and assessed the abuse or addiction rate is 3.27% for chronic pain patients with nonmalignant pain who were exposed to long-term opioid treatment (Fishbain, Cole, Lewis, Rosomoff, & Rosomoff, 2007).

The most serious adverse-effect of long-term opioid treatment is opioid-related overdose deaths. Annually, in the United States, there are more than 16,000 deaths of opioid-related causes (Kaplovitch et al., 2015). A recent study estimated the rates of opioid overdose death was 7.9 per 100,000 in 2013 and increased to 9.0 per 100,000 in 2014 (Rudd, Aleshire, Zibbell, & Matthew Gladden, 2016). This study also reports the increase in death rates for natural and semisynthetic opioids, which was 9% and 80%, respectively (Rudd et al., 2016). As opioid abuse and misuse, addiction, and overdose deaths increase, the related medical expenditures and societal costs also rise consequently.

1.1.3 Medical expenditures and economic burden of CNCP

The cost of opioid abuse is enormous in both in terms of medical care costs and other societal costs. There are many studies estimating the chronic pain and CNCP related medical utilization and expenditure (Chung, Zeng, & Wong, 2013; Gaskin & Richard, 2012; Hamza et al., 2012; Lam, Zheng, Davila, & et al., 2011; Maeng et al., 2017; Manchikanti et al., 2012; Riley, Eisenberg, Müller-Schwefe, Drewes, & Arendt-Nielsen, 2008; Dennis C Turk, 2002; Dennis C. Turk & Okifuji, 1998) (Kern et al., 2015) (Lam et al., 2011; Smith, 2010; Smith, Davis, Stano, & Whedon, 2013; Soni, 2011). According to Gaskin & Richard, the total US health care costs of pain is around $629 to $713 billion in 2008 inflated to 2017 dollar's value (Gaskin & Richard, 2012).

Based on the 2009 Medical Expenditure Panel Survey (MEPS), they estimated the money value of lost productivity for pain conditions is around $342 billion in 2017 dollar's value (Gaskin & Richard, 2012). The annual total direct health care cost and indirect social cost for pain conditions are greater than the annual cost of heart disease, cancer, and diabetes (Gaskin & Richard, 2012). However, the Gaskin and Richard's research was a general estimation for all pain conditions, which did not distinguish the expenditures between chronic pain and acute pain and did not assess the costs for different treatments.

The Agency for Healthcare Research and Quality (AHRQ) investigated the health care use and expenditures for adult women with pain conditions. Its statistical brief #342 shows that the average medical expenditures for women with pain conditions ($11,472 in 2017 dollars) were more than twice the expenditures for women without pain conditions ($4,741 in 2017 dollars) (Soni, 2011). Total health care expenditures for women for pain treatment were $12.9 billion ($14 billion in 2017 dollars) and total expenditures for prescription medicines to treat pain conditions among adult women were $2.4 billion ($2.6 billion in 2017 dollars) (Soni, 2011). Soni's report used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) diagnosis codes to identify pain condition measures, which might not precisely capture the chronic pain conditions. Also, Soni did not compare the difference in health care expenditures for opioid treatment as distinct from other treatments for pain conditions.

In a recent retrospective cohort study, Kern et al. investigate the treatment patterns, healthcare utilization, and treatment cost before and after initiation of opioid

treatment. Using claims data from 2007 till 2011, their study included around 2.9 million patients initiating opioid therapy. Most of the study patients (93%) had a duration of opioid therapy of 30 to 182 days, whereas 7% had long-term opioid therapy, defined as a duration of more than 182 days (Kern et al., 2015). Compared to the pre-opioid-therapy period, healthcare utilization increased during the first 6 months of opioid therapy, followed by a decrease after the first 6 months of therapy, though remaining higher than healthcare use before opioid treatment (Kern et al., 2015). Total all-cause costs followed a similar pattern., During the 12 months prior to initiation, costs were $13,459 ($13,900 in 2017 dollars) per patient/ per year, which increased to $31,695 ($32,724 in 2017 dollars) during the first 6 months of therapy, dropping to $ 20,705 ($21,384 in 2017 dollars) after first 6 months of therapy (Kern et al., 2015). One of the major cost drivers was inpatient hospitalization cost, which almost doubled from $7,911 ($8,170 in 2017 dollars) before initiation to $12,895 (13,318 in 2017 dollars) for the first 6 months of the opioid therapy (Kern et al., 2015).

A strength of this study is that it is based on large claims data with 4 years follow-up time to examine resource use and cost for individual patients before and after the initiation of opioid treatment, as well as the use of a study design that stratified patients into groups defined as short-term and long-term opioid therapy and weak and strong opioid users. Plus, the results of the study provided evidence of an increase in health care utilization and cost after the initiation of opioid treatment. However, the results should be interpreted carefully since it is an observational study, and as such the authors could not conclude whether the increase in utilization and cost was caused by

opioid therapy or other underlying confounders. Moreover, the data was from employer-provided health plans and conclusion can only apply to the similar demographic population. Additionally, for the estimation of opioid abuse and addiction, as well as the "doctor shopping", there is no extra data besides the claims record to assess the full impact of opioid abuse.

Some studies tried to evaluate the social and medical burden of opioid therapy related adverse-events, such as the cost of opioid abuse (Kirson et al., 2017; Scarpati et al., 2017), misuse and overdose death (Smith, 2010) (Maeng et al., 2017; McLellan & Turner, 2010; Modarai et al., 2013; Rudd et al., 2016). The office of national drug control policy estimated the economic cost of opioid drug abuse in the United States was at $193 billion in 2007 and $120 billion in lost productivity, $11 billion in healthcare costs, as well as $61 billion in criminal justice costs (Policy, 2011). Previous work has documented that opioid abusers are more likely to be associated with multiple comorbidities and their medical costs are 8 times higher than non-abusers ($15,884 vs. $1,830) (Manchikanti & Singh, 2008). Baser et al. used the 2006 to 2010 national Veterans Health Administration (VHA) data to estimate the annul healthcare cost for patients with opioid prescription, which is $25,197 vs. $6,350 without opioid prescription; and $28,882 for the patients with diagnosis of the opioid abuse vs. $13,605 for non-abuser (Baser et al., 2014). Meyer et al. did a literature review based on studies published during 2002- 2012, and found the annual additional health cost for private insured opioid abuser are from $14,054 to $20,546, and $5,874 to $15,183 for Medicaid opioid abuser (Meyer, Patel, Rattana, Quock, & Mody, 2014).

Kirson et al. tried to explore the drivers of the excess cost of opioid abuse over an 18-month study time by using private insurance administrative claims data (Kirson et al., 2017). The study identified opioid abuser and non-abuser and matched two groups using propensity scores adjusted for demographic, clinic, and health care resources utilization. The study compared the health care utilization and cost for abuser and non-abuser in three-time periods: baseline (7-12-month pre-abuse diagnosis), pre-index (1-6 months pre-abuse diagnosis), and 6 month post abuse diagnosis. The outcomes showed excess costs appeared 5 months before opioid abuse diagnosis and peaked at the first month after diagnosis (Kirson et al., 2017). The major driven factors for excess costs 5-month before diagnosis include non-opioid drug and alcohol abuse treatment (Kirson et al., 2017). And the excess cost driven factors for post-diagnosis include "opioid and other substance abuse disorder, mental health conditions, and painful conditions" (Kirson et al., 2017). The mean incremental healthcare cost is $14,810 per patient/ per year for opioid abuser.

They also did a 24-month follow-up analysis and the results showed during the extra 18-month follow-up period, the excess cost did not return to baseline level and raised up to $7,346 per patient/ per year (Scarpati et al., 2017). These studies suggest the opioid abuse related costs are also driven by other substance abuse even before the initial diagnosis of opioid abuse, and the excess cost will last for a more than 1-year follow-up time. Thus, the management of opioid treatment should be in the context of patient's history of substance abuse and should be followed for a longer time. However, these studies applied to all the opioid treatment, which did not distinguish the short or long-

term therapy, weak or strong opioid prescription, and for CNCP or for cancer related pain conditions.

Overall, there were some studies estimating the healthcare expenditures and social cost for the CNCP conditions and disclosed great burden caused by the conditions. Other studies compared total medical expenditures for groups with and without opioids treatments and showed associations between increase of healthcare utilization/ expenditure and initiation of opioid treatment (Kern et al., 2015; Soni, 2011). Additionally, some studies focused on the cost driven factors for opioid abuse and tried to assess the utilization and cost change pre and post the diagnosis of opioid abuse/misuse (Kirson et al., 2017; Scarpati et al., 2017). Nevertheless, these studies used private insurance claims data and could not represent the general population. There is one study that used 2008 national representative data (MEPS) to estimate the economic burden of pain in U.S. civilian noninstitutionalized population (Gaskin & Richard, 2012). Since MEPS is a self-reported survey data that might have potential authenticity problems for the answers of the survey questions, and the outcomes from this dataset have not been verified by other data sources, as well as no update since 2008. Besides, as many other studies, the estimation were based on the chronic pain patients and did not specify the study cohort as the CNCP patients. So, in my analysis, I will use both self-reported data and claims data to evaluation the health outcome and economic impact of CNCP conditions and opioid treatment for general population, in both cross sectional and longitudinal studies.

1.2 Research Plan

1.2.1 Research Questions

In this retrospective study, I examined total medical care use and expenditures for CNCP conditions based on the 2011 Medical Expenditure Panel Survey data and the 2008-2012 Texas Blue Cross and Blue Shield claims data. The research aims were to:

1) Compare the mean annual total healthcare utilization and overall healthcare expenditures for CNCP patients with and without opioids prescription/ therapy after the Propensity Score (PS) matching (MEPS data), and in the cross-sectional multivariate regression model (BCBS data)
2) Estimate annual total healthcare utilization and expenditures change for patients with new developed CNCP condition by the longitudinal model
3) Assessed annual total healthcare utilization and expenditures change for CNCP patients with new initiated opioid treatment episode by the longitudinal analysis

1.2.2 Conceptual Framework

In this retrospective cohort study, I identified patients with CNCP conditions using ICD diagnosis codes and SF-12 pain questions. I used emergency department (ED) visits and inpatients admission as the outcome measures to compare the healthcare utilization. I calculated total medical expenditure by summing all the payments from the individual's out-of-pocket payments and all third-party (insurance) payments.

To estimate the impact of CNCP condition and opioid treatment on total healthcare expenditure, I adopted Aday and Andersen's behavioral model of health service use as the conceptual framework (Andersen, 1995). This framework had been

used for numerous previous studies and validated in many different contexts for different health services and populations. According to the framework, the health expenditures associate with "predisposing, enabling, and perceived health need factors" (Andersen, 1995). The predisposing factors in my analysis included age, race, gender, education, health behaviors (smoke, exercise) and marital status. The enabling factors of my model were income, health insurance status, and location. The perceived health need factors adjusted for different health status and other chronic conditions that might influence the medical expenditure. I included self-reported health status (good, fair, poor) and hypertension, heart disease, emphysema, and diabetes as the enabling factors. The preliminary model included all the factors; but I only kept the statistically significant factors in the final model.

1.2.3 Data Source and Analytical Plan

This study used both self-reported survey data (CY2001-CY2011 MEPS) and private insurance claims data (CY2008- CY2012 Texas Blue Cross and Blue Shield). The MEPS data collected extensive information about health conditions, people's health behaviors, and health utilization and expenditures. It followed subjects for five panels in two years, which enabled the longitudinal analysis design. As a complement to the self-reported survey data, the Texas Blue Cross and Blue Shield claim data provided objective record for health conditions and utilization, which increased the validity and reliability of the results.

The cross-sectional analysis was based on a propensity score (PS) matching approach for the MEPS data to examine the difference of health care expenditures

between the opioids group and the non-opioids group adjusting for all known confounders. For the BCBSTX data, the expenditure was modeled by a GLM model with log link gamma distribution to assess the impact of independent variables due to the right skewed distribution for medical expenditure.

For the longitudinal analysis, I adopted the generalized linear mixed-effects model (GLMMs) for mass-univariate data. The GLMMs allowed both fixed and random effects treating patient-specific intercepts and linear change with time as random effects. This approach allowed me to assess the long-term opioid treatment (the key fixed effect) on the average change in total annual medical expenditure while accounting for the dependence of within-patient repeated measures over time.

The mixed-effect models included age (continuous), sex (male and female), race (white, black, Hispanic and other), marital status (married or not), poverty level (low and middle/high income), education (high school or less and college or higher), insurance (any private insurance, any public insurance, and uninsured), smoking (yes or no), MSA (yes or no), BMI (underweight, normal, overweight, and obesity), health status (excellent, very good, good, fair, and poor), comorbidity (high blood pressure, heart disease, stroke, emphysema, chronic bronchitis, asthma, high cholesterol, diabetes, joint pain, and arthritis), treatment status (treatment or control group).

Based on previous studies, all the data for medical expenditure were presented as least-squares means (95% confidence interval [95% CI]). There was less covariates adjustment for BCBSTX data, due to the data limitation.

The expected outcomes included the difference of health expenditure among CNCP patients with long-term opioid treatment group and non-opioid treatment group. The results would be informative for the policy makers, insurance payers, physicians, as well as the patients to balance the need of treating chronic pain and minimizing the risk of opioid treatment, avoiding unnecessary health expenditure.

CHAPTER 2. UTILIZATION AND COST ANALYSIS OF MEPS

In this chapter, I used 2011 MEPS data to compare the annual total health expenditure for CNCP patients with and without long-term opioid treatments. The main research question was to assess whether there were higher health expenditures for patients receiving long-term opioid treatment, and the scale of the difference. In order to compare the opioid and non-opioid samples while adjusting for demographic, SES and clinical characteristics, I adopted the Propensity Score (PS) matching approach and adjusted for age, gender, race, marital status, poverty level, education, insurance, smoking behavior, physical activity, MSA, BMI, and comorbidity status. These covariates were compared before matching and after matching to evaluate the successfulness of the PS matching algorithm, and finally the average treatment effect of opioids use on health expenditure was estimated based on the matched samples.

2.1 Data

2.1.1 Overview of MEPS Data

Conducted by the Agency for Healthcare Research and Quality (AHRQ) and the National Center for Health Statistics, MEPS is a nationally representative survey for health care use, expenditures, sources of payment, and health insurance coverage of the U.S. civilian non-institutionalized population since 1996. The MEPS data adopts an overlapping panel design. Each panel of respondents is surveyed through five rounds in two years. MEPS has the Household Component (HC) which draws samples from prior

years' National Health Interview Survey, and the Insurance Component (IC) which collects data from Health Insurance Cost Study. Each year, MEPS selects one new panel of survey respondents. Each panel has several rounds of surveys covering during two full calendar years (see Figure 1). This design assures the continuous presence of repeated survey measures in the MEPS data, which is essential for estimation of the expenditure model. (The data for generating the figure 1 was retrieved from https://meps.ahrq.gov/survey_comp/hc_data_collection.jsp)

Figure 1 MEPS Panel Design: Data Reference Periods.

The 2011 MEPS data covered the Round 3 and 4 for MEPS Panel 15 and Round 1, 2 and 3 for Panel 16. The combined 2011 MEPS provided a nationally representative

sample of the civilian noninstitutionalized population of the United States in this calendar year. The sample was based on complex stratified multi-stage probability design to represent national population. The unweighted response rate was 54.9%. The MEPS data assigned a person-level weight to each survey participant to adjust the nonresponse and population features.

This study used both the Household Component (HC) and Medical Provider Component (MPC). The MEPS-HC included demographic characteristics, health expenditures, health conditions, health status, utilization of medical services, access to care, health insurance coverage, and family and individual income, among other variables. The sample contained 13,449 households and 33,622 individuals' records.

Additionally, by directly collecting data from respondents' providers and pharmacies, the MEPS-Medical Provider Component files provided detailed expenditure information of medical events and pharmacy records.

The 2011 Medical Conditions file (HC146) contained reported current medical conditions for the survey sample in the calendar year. If a condition had not been diagnosed before the survey data or was currently experienced, it was defined as the current condition. The file contained 108,619 medical records and 35 variables, including the ICD-9 diagnosis and procedure codes, as well as the clinical classification codes, which were aggregated and mutually exclusive clinical classification category codes. The 2011 Prescribed Medicines file (HC-144A) recorded 3,123,747 unique prescribed medicine events and associated expenditures, as well as the medical conditions.

2.1.2 MEPS Sample selection

To generate the sample for this analysis, I merged the Medical Conditions file (HC-146) and Prescribed Medicines file (HC-144A) with the person-level MEPS-HC dataset, by using the MEPs linked files. After merging, I applied the following inclusion and exclusion restrictions: the primary inclusion criteria related to identifying patients with diagnosis codes indicative of all chronic pain conditions, and the main exclusion criteria were a current diagnosis of cancer or a prior cancer condition which was defined as with ICD-9 diagnosis code of 140.00-209.36, 209.70-209.79, 511.81, 789.51 (ICD9Data, 2012). Also, for the opioid treatment, I used the prescription files to flag prescriptions for all opioid drugs. The flow-chart figure 2 in the result section showed the sample selection process.

To fully capture all the CNCP conditions, I used both self-reported chronic pain condition from survey sections in the MEPS, and the claim records for the CNCP diagnosis from the medical event file. For the self-reported CNCP, there were two sources: SF-12 questionnaire (Antaky, 2016) and the Priority Conditions section of the MEPS-HC Questionnaire Sections. For the claim medical event record, all the CNCP were identified by ICD-9 diagnosis code.

In the MEPS-HC SF-12 questionnaire, there was the pain related question "During the past 4 weeks, how much did pain interfere with your normal works including work outside the home and housework. The options were: extremely, quite a bit, moderately, a little bit, and not at all (AHRQ, 2013). This question had been asked twice at round 4 in Panel 15 and round 2 in Panel 16 and generated a variable

ADPAIN42, of which the value reflects the answers in both rounds. If the answer was extremely, quite a bit, or moderately, it was considered a chronic pain condition (AHRQ, 2013).

The other self-reported CNCP condition was captured by the answer of Priority condition survey joint pain questions, which asked if the person (aged 18 or older) had experienced pain, swelling, or stiffness around a joint in the last 12 months (AHRQ, 2013). This question had been asked twice at round 3 in Panel 15 and round 1 in Panel 16, also at round 5 in Panel 15 and round 1 in Panel 16. Any "yes" answer to this question was coded as chronic pain conditions (AHRQ, 2013).

Additionally, the study selected CNCP conditions by using the ICD-9 diagnosis codes and HCPCs/CPT codes from the medical events files. The patients were flagged as CNCP as long as they had one of the following ICD-9 diagnosis code in in table 1 and one of the HCPCs code. All the codes to flag CNCP conditions were from previous studies (Cardarelli et al., 2017; Chang, Ma, Lee, & Hsieh, 2015).

Table 1 ICD-9 Diagnosis codes and HCPCs codes to flag CNCP conditions.

ICD-9 Diagnosis code	
Code	Description
338.x	Pain, Not Elsewhere Classified
524.62	TMJ Arthralgia
569.42	Anal or Rectal Pain
524.x	Dent Facial Anomalies Including Malocclusion
595.x	Cystitis
617.x	Endometriosis All
625.x	Pain and Other Symptoms Associated with Female Genital Organs
711 -714	Arthritis
715.x	Osteoarthritis
716.6-716.9	Monoarthritis Arthropathy
716.91	Arthropathy Nos-Shlder
716.97	Arthropathy Nos-Ankle
719.41	Joint Pain-Shlder
719.43	Joint Pain-Forearm
719.45	Joint Pain-Pelvis
719.46	Joint Pain-L/Leg
719.47	Joint Pain-Ankle
719.49	Joint Pain-Mult Jts
720.0x–721.3x	Ankylosing Spondylitis and Other Inflammatory Spondylopathies
72210	Lumbar Disc Displacement
722.0x,	Displacement of Cervical Intervertebral Disc Without Myelopathy
722.32,	Schmorl'S Nodes
722.52,	Degeneration of Lumbar or Lumbosacral Intervertebral Disc
722.73,	Intervertebral Disc Disorder with Myelopathy, Lumbar Region
722.83,	Postlaminectomy Syndrome, Lumbar Region
722.93,	Other and Unspecified Disc Disorder, Lumbar Region
723.1	Cervicalgia
724.1	Pain in Thoracic Spine
724.2	Lumbago
724.3	Sciatica
724.5	Backache Nos
724.02,	Spinal Stenosis, Lumbar Region, Without Neurogenic Claudication
724.2x,	Lumbago
724.3x,	Sciatica
724.6x	Disorders of Sacrum
724.7x	Chronic Lower Back Pain
725	Polymyalgia Rheumatica
726.33	Olecranon Bursitis
726.71	Achilles Tendinitis
7270.6	Tenosynovitis Foot/Ankle
728.85	Spasm of Muscle
729	Fibromyalgia
729.x	Other Disorders of Soft Tissues

Table 1 (continued)

ICD-9 Diagnosis code	
729.1	Myalgia and Myositis Nos
729.5	Pain in Limb
729.82	Cramp in Limb
729.89	Muscskel Sympt Limb Nec
780.7	Malaise and Fatigue
784.1	Throat Pain
784.92	Jaw Pain
780.x	General Symptoms (Symptoms, Signs, And Ill-Defined Conditions 780-799)
840.4	Sprain Rotator Cuff
840.8	Sprain Shoulder/Arm Nec
840.9	Sprain Shoulder/Arm Nos
841.8	Sprain Elbow/Forearm Nec
847	Sprain of Neck
847.2	Sprain Lumbar Region
848.8	Other Sprains Strains
842	Sprain of Wrist Nos
845.09	Sprain of Ankle Nec
845.1	Sprain of Foot Nos
845.19	Sprain of Foot Nec
HCPCs code (ICD-9 with one of the following)	
99201-99205	Evaluation and Management
99212-99215	Evaluation and Management
99241-99245	Evaluation and Management
99385	Evaluation and Management
99387	Evaluation and Management
99395-99397	Evaluation and Management
99402-99404	Evaluation and Management

Last, in order to exclude the cancer patients, the study eliminated all individuals with prior cancer conditions or a current diagnosis of a variety of cancer. The current diagnosis of cancer was identified by the ICD-9 codes and the MEPS Clinical Classification Codes (CCCODEX). The ICD-9 cancer diagnosis code was flagged by the

CMS definition, of which the ICD-9-CM range for cancer was 140.00-209.36, 209.70-209.79, 511.81, 789.51. The MEPS CCCODEX code was generated by aggregate the ICD-9 diagnosis code to mutually exclusive categories. The cancer condition is in the CCCODEX range 11-45 (Chang, Ma, Lee, & Hsieh, 2015).

2.2 Methods

The objective of the analysis in this chapter was to estimate the differential in medical expenditures associated with the presence or absence of prevalent opioid treatment among patients with CNCP, accounting for differences in patient characteristics that might affect utilizations and medical expenditures.

2.2.1 Medical Expenditures

Medical expenditure in MEPS referred to payments for health care services including individuals' out-of-pocket payments, private insurance payments, Medicaid, Medicare and other payment sources for all inpatient, outpatient, and professional services, as well as for pharmaceuticals and devices. MEPS data excluded payments for over-the-counter drugs. In this study, total health care expenditures were the sum of expenditures for office visits, hospital outpatient visits, ambulatory visits, hospital emergency room visits, hospital inpatient stays, and prescribed medicines, as well as other medical equipment, devices and services.

2.2.2 Current Opioid Use

Opioid drugs were categorized using national drug codes (NDC). The drugs were considered as opioid treatments including Buprenorphine, Butorphanol, Codeine,

Dihydrocodeine, Fentanyl, Hydromorphone, Levomethadyl, Levorphanol, Meperidine, Methadone, Morphine, Opium, Oxycodone, Oxymorphone, Pentazocine, Propoxyphene, Tapentadol, Tramadol. The final opioid prescriptions list included 13,270 opioid drugs (NIDA, 2018), which could be downloaded from http://www.pdmpassist.org/pdf/Conversion%20Reference%20Table.xlsx. Current opioid users were defined as patients with prescription of continuously opioid drugs more than 3 months in calendar year 2011. Non-opioid users were defined as patients with no opioid prescriptions or less than 3 months continues opioid prescription in 2011.

2.2.3 Covariates

The medical expenditure comparison between opioid user group and non-opioid user group needed to consider the impact of some medical conditions/ comorbidities, demographic factors and socioeconomic status. Also, CNCP as the major predictor was often affected by psychological and socio-environmental factors (Furlan et al., 2006). In this paper, to adjust for the potential confounders, I included following covariates: gender, age, race/ethnicity, marital status, education, income, insurance status, MSA residents or not, smoking status, physical activity, weight and obesity, general health status (excellent, very good, good, fair, and poor), and eight health conditions indicators: high blood pressure, heart disease, stroke, emphysema, chronic bronchitis, high cholesterol diagnosis, diabetes, and arthritis.

2.2.4 Statistical Analysis

In the comparison of medical expenditures between the opioid treatment group and non-opioid treatment group, I adopted the propensity score (PS) approach to address

potential confounding related to treatment selection (i.e., CNCP patients treated with opioids might have more severe pain than those not treated with opioids). The PS approach entailed estimating the likelihood that a CNCP pain patient received opioid treatment based on the patient's observed characteristics. The fundamental assumption of the PS method is "Strong Ignorability" (Rosenbaum & Rubin, 1983), which assumes that observed baseline covariates were sufficiently comprehensive, so that the impact of any unobserved confounder was small enough to be ignored for both treatment assignments and outcomes (Rosenbaum & Rubin, 1983).

Thus, the propensity score for each patient was determined by a treatment assignment logistic regression model, where the dependent variable was the receipt of opioids (yes or no), and the independent variables were assumed to affect both opioid treatment choice and medical expenditure outcomes, specifically age, gender, race/ethnicity, marital status, education, income, insurance status, smoking status, physical activity, weight and obesity, diabetes, asthma, general health status, and MSA region indicators.

CNCP individuals with and without opioid treatment were matched according to propensity scores. After running bivariate test of each matching variable and treatment variable, the next step was to create the propensity score by log odds of predicted probability, followed by checking the balanced propensity score across opioid and non-opioid groups. The PS matching was conducted using STATA/PSMATCH2 and based on nearest neighbor matching within caliper and without replacement (Leuven & Sianesi, 2018). As recommended by Rosenbaum and Rubin, a caliper size equal to one

quarter of the standard deviation of the propensity score distribution for the entire study sample was used (Rosenbaum & Rubin, 1985).

After matching, I assessed the matching quality by using standardized bias and Standardized Mahalanobis metric distance. For continuous variables, the standardized difference in % was calculated to reflect the difference of mean between two groups for each covariate, which was

$$d = 100\frac{(\overline{x_p} - \overline{x_t})}{\sqrt{\{(S_P^2 + S_t^2)/2\}}}$$

where for each covariate $\overline{x_p}$ and $\overline{x_t}$ are the sample means and S_P^2 and S_t^2 are the corresponding sample variance (Rosenbaum & Rubin, 1985). For dichotomous variables, the standardized difference is defined as:

$$d = 100\frac{(p_p - p_t)}{\sqrt{\{(p_p(1-p_p) + p_t(1-p_t))/2\}}}$$

where p_p is the proportion of treatment group and p_t is the proportion of control group.

Also, for categorical variables with K levels, I adopted a multivariate Mahalanobis distance method to generalize the standardized difference metric to handle a multinomial sample (Stuart, 2010). Let

$$\mathrm{T} = (\widehat{P_{12}}, \widehat{P_{13}}, \dots \widehat{P_{1k}})'$$

$$\mathrm{C} = (\widehat{P_{22}}, \widehat{P_{23}}, \dots \widehat{P_{2k}})'$$

$$\widehat{P_{1k}} = \Pr(\, Category\ k \mid Treatmet\ group\ j)$$

$$j \in \{1,2\}$$

$$k \in \{2,3, \dots, K\}.$$

The standardized Mahalanobis metric difference is then defined as

$$d = \sqrt{(T - C)' S^{-1} (T - C)}$$

where S is a $(k - 1) \times (k - 1)$ covariance matrix, which is defined as

$$S = [S_{kl}] = \begin{cases} \dfrac{[\hat{P}_{1K}(1 - \hat{P}_{1K}) + \hat{P}_{2K}(1 - \hat{P}_{2K})]}{2}, & k = l \\ \dfrac{[\hat{P}_{1K}\hat{P}_{1l} + \hat{P}_{2K}\hat{P}_{2l}]}{2}, & k \neq l \end{cases}$$

The empirical criterion of excellent matching was standardized bias less than 5%, while bias less than 10% generally was considered adequate (Austin, 2011, p. 412).

Based on the matched sample, bivariate analyses were used to establish demographic and clinical variables associated with the outcome. Differences between groups were assessed with $\chi 2$ or Fisher's exact test for categorical variables, and Student t-test or Wilcoxon rank-sum test for continuous variables.

2.3 Results

The original 2011 MEPS data included 35,313 individuals. After excluding individuals with the prior condition of cancer and current diagnosis of cancer, there were 33,158 people. By using the SF-12 questionnaire and ICD-10 code, I identified 11,858 people in the final CNCP sample, of which 979 individuals had opioid treatments. Figure 2 shows the sample selection flowchart.

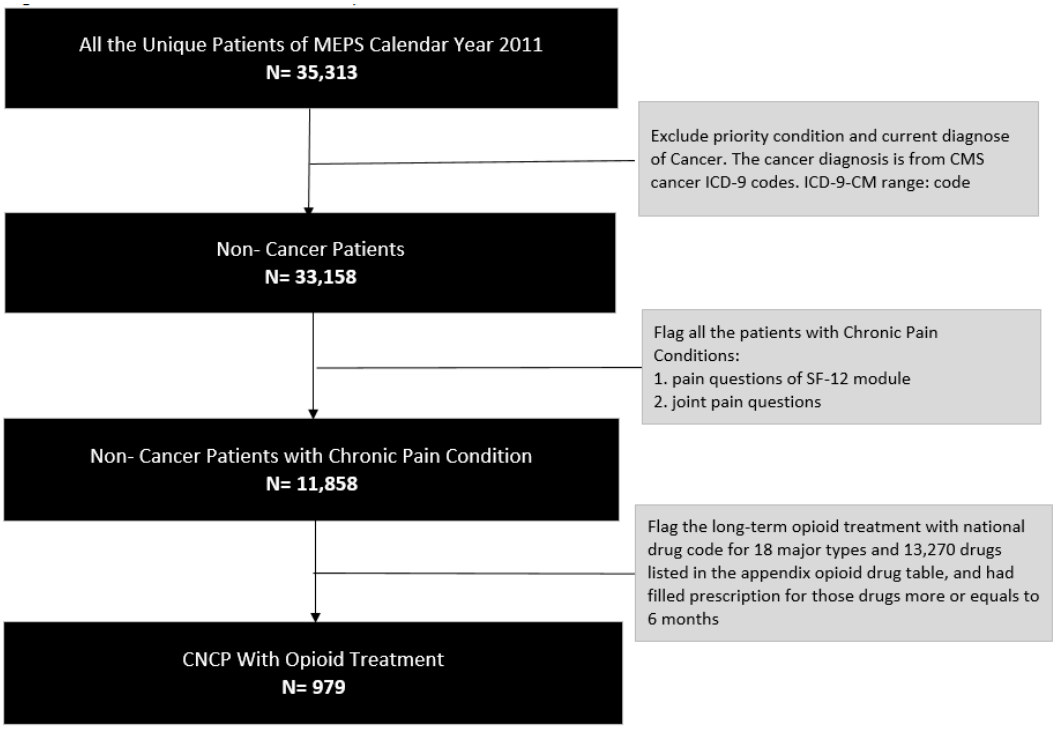

Figure 2 MEPS Cross-sectional Analysis Cohort Selection Flowchart.

The table 2 showed the results of propensity score before and after PS-match covariate balance (bias) statistics, and the comparison of each covariate between individuals using or not using opioids treatments. Before matching, there were 11,503 individuals in non-opioid treatment group and 979 in treatment group. All 979 treatment patients were patients were matched to 979 patients from the pool of patients in the non-opioid treatment group. Table 2 included the mean or percent comparison of all the covariates for opioid and non-opioid groups before PS matching. There were several covariates statistically significant different between treatment and control group before the PS-match, which included race, married or single, income level, insurance type,

smoking status, physical activity, and some chronic conditions. The standardized difference for those covariates ranged from 4% to 54%. The initial differences between opioid and non-opioid groups were large.

Table 2 A Group Comparison before PS matching for MEPS Cross-sectional Analysis.

	Non-Opioids (n=11,503)	**Opioids (n=979)**	**Two-sample t-statistics**	**Distance****
Variables	Mean Or %	Mean Or %	P-value	in %
Age	46.49	49.31	0.01	15%
Gender				
Female	58%	56%	0.54	4%
Race/ Ethnicity*				
White	49%	56%		
Black	21%	25%		
Hispanic	22%	11%		
Other	8%	8%	0.00	29%
Marital Status*				
Married	63%	58%	0.02	
Poverty/Income*				
Poor/ Low	45%	49%		
Middle/High	55%	51%	0.04	9%
Education				
High School or less	63%	57%		
College or Higher	37%	43%	0.23	11%
Insurance*				
Any Private Insurance	55%	56%		
Any Public Insurance	31%	34%		
Uninsured	14%	10%	0.02	17%
Smoking*	21%	30%	0.00	6%
Physical Activity*	45%	36%	0.00	
BMI				
Underweight	3%	2%		
Normal Weight	28%	25%		
Overweight	32%	33%		
Obesity	37%	40%	0.59	19%

Table 2 (continued)

Variables	Non-Opioids (n=11,503) Mean Or %	Opioids (n=979) Mean Or %	Two-sample t-statistics P-value	Distance** in %
MSA	85%	84%	0.33	
High Blood Pressure	16%	13%	0.24	
Heart Disease*	18%	26%	0	
Stroke*	5%	11%	0	
Emphysema *	3%	5%	0.02	
Chronic Bronchitis*	5%	8%	0.04	
Asthma	12%	15%	0.05	
High Cholesterol	39%	41%	0.42	
Diabetes	16%	15%		
Joint pain*	79%	85%	0.04	
Arthritis*	39%	61%	0	44%
Health Status*				
Excellent	13%	5%		
Very Good	34%	24%		
Good	34%	31%		
Fair	16%	28%		
Poor	3%	12%	0	54%

*P-value<0.05

**The difference measure is the mean difference as a percent of the average standard deviation for continuous or dichotomous variables and as the standardized Mahalanobis metric distance for K-level categorical variables

After estimating the propensity scores, the box-plots in Figure 3 showed the difference for two groups before matching. The range of the propensity score for the opioid group was much wider than the range for the non-opioid group, but there was considerable overlap in the two distributions which provides a broad range of support for propensity score matching.

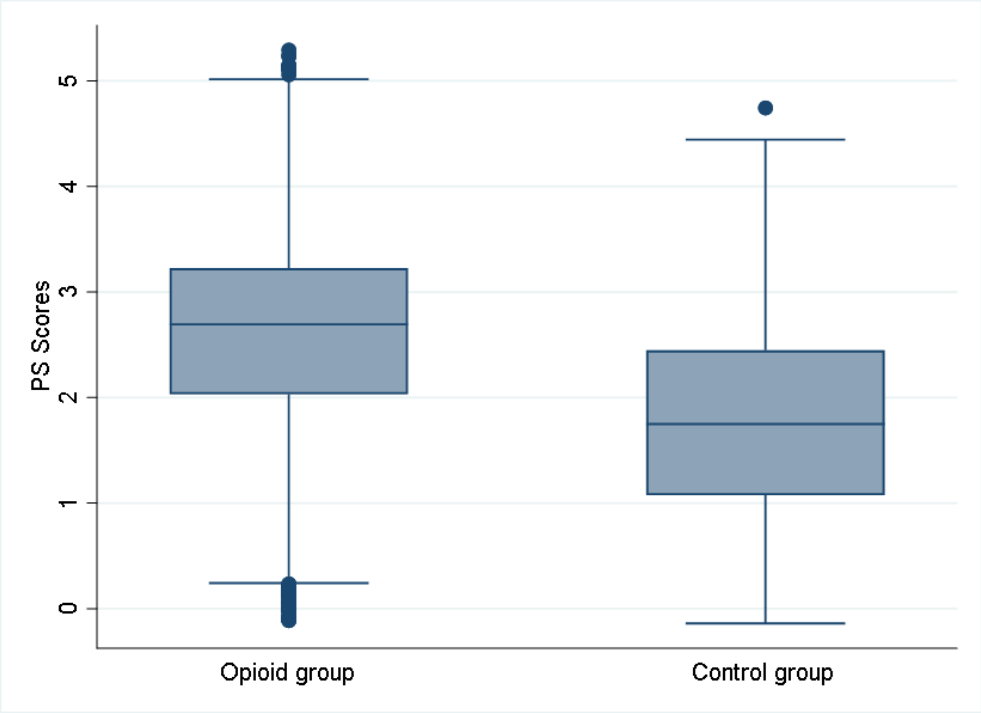

Figure 3 Boxplots of Estimated PS Scores.

Similar as the table 2, the table 3 included the mean or percent comparison of all the covariates for opioid and non-opioid groups after PS matching. There were several covariates statistically significant different between treatment and control group after the PS-match, which included race, married or single, income level, insurance type, smoking status, physical activity, and some chronic conditions. The standardized difference for those covariates ranged from 4% to 43%. The after matching differences between opioid and non-opioid groups were reduced, but balance remained poor for some individual covariates, particularly for arthritis, which is the comorbid condition most directly related to the need for long-term opioid treatment.

Table 3 A Group Comparison after PS matching.

	Non-Opioids (n=979)	Opioids (n=979)	Two-sample t-statistics	Distance
Variables	Mean Or %	Mean Or %	P-value	in %
Age	49.75	49.82	0.93	4%
Gender				
Male	42%	44%		
Female	58%	56%	0.54	5%
Race/ Ethnicity*				
White	50%	48%		
Black	22%	24%		
Hispanic	20%	19%		
Other	8%	9%	0.00	24%
Marital Status*				
Current Married	50%	44%		
Current Single	50%	56%	0.02	8%
Poverty*				
Poor/ Low income	44%	49%		
Middle/High income	56%	51%	0.04	4%
Education				
High School or less	60%	57%		
College or Higher	40%	43%	0.23	13%
Insurance*				
Any Private Insurance	57%	57%		
Any Public Insurance	28%	33%		
Uninsured	15%	10%	0.02	9%
Smoking	21%	30%	0	5%
Physical Activity*	45%	36%	0	
MSA	85%	84%	0.33	
BMI				
Underweight	2%	2%		
Normal Weight	28%	25%		
Overweight	33%	33%		
Obesity	38%	41%	0.59	16%
High Blood Pressure	16%	13%		19%
Heart Disease*	18%	26%	0.03	11%
Stroke*	5%	11%	0.02	10%
Emphysema *	3%	5%	0.02	10%

Table 3 (continued)

Variables	Non-Opioids (n=979) Mean Or %	Opioids (n=979) Mean Or %	Two-sample t-statistics P-value	Distance in %
Chronic Bronchitis*	5%	8%	0.04	4%
Asthma	18%	15%	0.05	10%
High Cholesterol	20%	15%	0.42	14%
Diabetes	16%	15%	0.59	3%
Joint pain*	79%	85%	0.04	14%
Arthritis*	39%	41%	0	43%
Health Status*				
Excellent	11%	9%		
Very Good	33%	38%		
Good	35%	31%		
Fair	18%	19%		
Poor	3%	4%	0.1	13%

*P-value<0.05

Table 4 provides summary of the percent reduction in bias for categories of covariates after the matching. Matching reduced the bias for age by 73%, 88% for gender, 39% for race, 67% for marital status, 11% for poverty and 18% for education. There also was a decrease in bias for the health-related covariates, such as comorbidities and health status. There was adequate covariate balance for most of the categories of covariates. Overall, the PS-matching substantially reduced bias across groups.

Table 4 Reduction % in Bias for Demographic Variables.

	Initial Bias	Bias after matching	Per cent** reduction
Age**	15%	4%	73%
Race/Ethnicity**	29%	14%	52%
Marital Status*	11%	8%	27%
Poverty*	9%	4%	56%
Insurance*	17%	9%	47%
Comorbidities**	28%	8%	71%
Health**	54%	13%	76%

*Compared the reduction of Standardized Mahalanobis metric distance
**P-value<0.05

I compared total medical expenditures between the opioid and non-opioid groups in the propensity-score matched sample (Table 5). Compared with non-opioid uses, those prescribed opioids had higher medical expenditures across every category of medical spending. The sample mean of total annual medical expenditures were $23,413 for the opioid group and $8,969 for non-opioid groups with $14,444 difference. Hospital inpatient stays, hospital outpatient visits and prescribed medicines were the three-major driven components for the expenditure difference. These differences were from PS matched samples, which adjusted to demographic or clinical characteristics that differ between opioid and non-opioid users.

Table 5 Comparison of Different Types of Medical Expenditures for PS-Matched CNCP sample.

Variables	Opioids (n=979) $ Mean (S.D.)	Non-Opioids (n=979) $ Mean (S.D.)	$Difference
Total Medical Expenditures*	23,413 (43,057)	8,969 (27,185)	14,444
Office Visits *	2,440 (4,368)	1,142 (3,466)	1,298
Hospital Outpatient Visits *	3,833 (12,601)	1,304 (5,733)	2,529
Ambulatory Visits*	418 (1,689)	200 (1,004)	218.7
Hospital Inpatient Stays*	11,192 (37,066)	4,265 (23,788)	6,927
ED Visits *	1,106 (3,506)	572 (3,434)	534.3
Prescribed Medicines*	3,536 (7,315)	1,256 (3,190)	2,280
Home Health Care	886 (5,864)	231 (1,888)	421

*P-value<0.05

2.4 Discussion and Limitations

Based on the MEPS data, this analysis estimated the impact of opioid treatment on healthcare expenditure. The unadjusted yearly average total health expenditure was $23,413 higher for opioid group than non-opioid group. To further breakdown, the difference was mainly from hospitalizations, outpatient visits and prescriptions. Although, there had been no same model specification published yet, this estimation was consistent with other similar study (Kern et al., 2015). In Kern et al.'s paper, they tracked CNCP patients' health expenditure before and after the initiation of long-term opioid treatment. Their estimation were around $20,000 dollars increase after the initiation, which was close to my outcomes. Both Kern et al.'s study and this study found inpatient expenditure was the major cost driven factor for opioid treatment group.

There was no previous cross-sectional analysis that compared the overall annual health expenditure between long term opioid treatment group and non-opioid treatment group for CNCP patients. The finding showed huge difference for these two groups with PS matching for covariates. However, there were some limitations. First, the MEPs data is a self-reported database, which might have the subjective-bias problem. The participants of the survey might report incorrect information. However, the MEPs has been used in many studies and the quality of data has been validated. Moreover, to validate the findings, I used private insurance claims data to replicate this analysis in chapter 4.

A second limitation is that the sample selection was based on the propensity score matching approach. The matching was on the known confounders, which might not include all the potential confounders, however we only could include all the variables that we had. And the after-matching sample, there was an adequate reduction of bias for many potential confounders, but overall the reduction in bias was not sufficient to assure the comparison was "apple-to-apples."

Last but not least, the comparison was at calendar year level, I did not investigate the expenditure at different timeframes, such as the comparison at 6-month after initiation of opioid treatment, 12-month, and 24-month. And there was no comparison for CNCP patients' health expenditure change before and after the opioid treatment. Next chapter was the longitudinal analysis for the expenditure comparison among CNCP patients before and after opioid and opioid treatment as well as the incremental cost associated with the diagnosis of CNCP condition.

2.5 Conclusion

In the national opioid crisis, it would be informative to not only understand the effectiveness of the opioid treatment, but also the potential cost of treatment. It is critical to investigate the health expenditure difference for opioid treatment when there has been lack of evidence to prove the long-term opioid treatments for CNCP as the best practice. This chapter investigated the health expenditure difference among CNCP patients with and without opioid treatment. By using MEPs data, I conducted the expenditure comparison for the PS matched sample. The outcomes showed the opioid treatment group had almost 3 times higher health expenditure compared to non-opioid treatment group. There were some limitations of this cross-sectional analysis, but the estimation was aligned with other studies. This huge health expenditure difference is mainly driven by inpatient and outpatient visits, as well as prescriptions.

Although there are some limitations of this analysis, the outcomes gave policy makers, payers, physicians, and CNCP patients insights about potential expenditure difference with and without the opioid treatment. Different from other studies focused on certain types of chronic pain, this estimation was for all types of CNCP by using both ICD diagnosis code and SF-12 Questionnaire. Policy makers could use this estimation to assess the social cost for the opioid treatment and accordingly make change of the opioid management. Payers could use this outcome to adjust the reimbursement. Physicians could share this information with patients to help patient deciding on an appropriate CNCP management strategy. My results underscore the high cost of opioid treatment to the health care system and highlight the need for cost-effective CNCP treatments.

CHAPTER 3. THE LONGITUDINAL ANALYSIS OF MEPS

In the previous chapter, I used one-year MEPS data to compare the health expenditure for CNCP patients with and without long-term opioid treatments. The outcomes reveled great increase of health expenditure for long-term opioid treated patients. In order to confirm the difference was associated with opioid treatment rather than other health conditions or demographic factors, I adjusted the model by including covariates of gender, age, race, income, education, marital status, insurance types, and several health conditions. The final regression model showed that the health expenditure for opioid treatment group was 3 times higher than the non-opioid treatment group. Even though I did PS matching and multi-variable regression to avoid potential confounders, I only adjusted for known covariates. To further investigate the correlations between the higher health expenditure and the opioid treatment, I conducted a longitudinal analysis in this chapter. The strength of longitudinal study was to collect consistent data at a personal level, which excluded various background variables that could affect data outcomes.

3.1 Introduction

By using 10 years MEPs data, I took advantage of the panel data feature of MEPS to conduct the longitudinal study to explore the relationship between the opioid treatment and change of health expenditures. One study used the MEPS data did a longitudinal analysis to check the incremental cost for chronic pain condition (Henschke

et al., 2015). But no previous studies adopted longitudinal design to estimate annual health expenditure changes for initiation of new long-term opioid treatment on CNCP patients. There were two major research questions: 1) what was the change of annual health expenditures after new diagnosis of CNCP conditions? 2) what was the change of annual health expenditure for CNCP patients starting a new episode of opioid treatment?

3.2 Data

The data was from the calendar year 2000-2011 Household Component of the MEPS, which were HC-065 panel 5:2000-2001, HC-080 panel 7:2002-2003, HC-098 panel 9:2004-2005, HC-114 panel 11:2006-2007, HC-130 panel 13:2008-2009, HC-148 panel 15:2010-2011 (AHRQ, 2018). MEPS sampled a new panel of households annually and tracked each panel for additional year. For each panel, MEPS gathered health and related expenditure information of everyone in the households during 5 rounds interviews in the 2-year timeframe. All round 1 interview begun on February and ends on June of the first year, followed by round 2, which finished within 12-month period after the first interview. The round 3, 4 and 5 interviews were finished during the second year. So, for each panel, the final consolidated data included a full 2 years of records for each patient.

I combined ten years MEPS longitudinal cohort to test the difference of expenditure for new developed CNCP patients before and after CNCP diagnosis, and the increase of medical expenditure caused by new opioid treatment for established CNCP patients. Since MEPS had two calendar years of data for each panel, it was possible to

identify the new diagnosed CNCP patients inside of each panel over 6 panels, as well as to track CNCP patients' new episode of long-term opioid treatment.

This study also used the MEPS Medical Conditions Files to capture household-reported medical conditions. The medical conditions information was reported during the first year of the 2-year panel. I merged it into the longitudinal cohort. The final cohort exclude individuals younger than 18 years old by using the MEPS Self-Administered Questionnaire (SAQ) eligible participates. The SAQ was part of the Household Component, which was given to all household respondents at least 18 years old during round 2 and round 4 (AHRQ, 2018).

Among the adult patients, I excluded all the cancer patients, which were identified by ICD-9 diagnosis code and the health condition files same as the previous chapter. Then, CNCP patients were flagged by ICD-9 diagnosis code and the answer of the SF-12 questioner same as the cross-sectional analysis to flag CNCP patients.

3.3 Methods

3.3.1 Measurements

3.3.1.1 Dependent variables

The dependent variable was the annual health care expenditure which included payments from third-party payers and self-out-of-pocket payments. The total health expenditure could be broken down by services types, where were inpatient expenditure, outpatient expenditure, prescriptions expenditure, emergency department visits expenditure, office visits expenditure and others (medical supplies and equipment, home

health care expenditure, dental, vision care expenditure and so on). The total expenditure was adjusted for inflation by the Consumer Price Index (CPI) to transfer to 2011 dollars (BLS, 2018).

3.3.1.2 Predictor variables

For the first research question: health expenditures after new diagnosis of CNCP conditions, the primary predictor variable was new diagnosis of CNCP conditions. The definition of new diagnosis was that patients did not have CNCP conditions in the first year and had CNCP conditions in the second year. The CNCP conditions were flag by both ICD-9 diagnosis code and survey questions, same as the previous chapter.

For the second research question: the health expenditure for CNCP patients starting a new episode of long-term opioid treatment, the primary predictor variable was new episode of long-term opioid treatment, which was captured for CNCP patients that did not have opioid treatment in the first year and started long-term opioid treatment in the second year. The opioid treatment was flagged by the same NDC code as previous chapter.

3.3.1.3 Model Covariates

The longitudinal design of this chapter tracked the same cohort pre- and post-CNCP diagnosis/ opioid treatment, to show the expenditure changes. The model excluded the difference for many characteristics at individual level. But at population level, there still could have other confounders influencing the relationships between predictor variables and expenditures. Other studies proposed some potential cofounders

for adjustment (Gaskin 2011, Richard 2012), which included demographic, social economics status, geographic location, and health conditions.

In my model, I included age (continuous), gender (male and female), race (white, black, Hispanic, and other) and marital status (married or not) as the demographic covariates. For the socioeconomic covariates, I included education (high school or lower, and college or higher), household income level (poverty or not), insurance types (any private insurance, any public insurance, and uninsured). For the geographic variance, I included Metropolitan Statistical Area (MSA) yes or no. For the health conditions, I included three types of covariates: health behaviors variables (smoking or not and physical activity or not), health status variables (excellent, very good, good, fair, and poor), and chronic condition variables (high blood pressure, heart disease, stroke, emphysema, chronic bronchitis, asthma, high cholesterol, diabetes, joint pain, and arthritis, as well as the body mass index (BMI). The health status variables were from self-reported health questioner SF-12. The answer for general health was used to reflect the health status. However, due to the pain related questions in the self-reported questioner were used in the CNCP flag, the covariates did not include them. Since the chronic condition cancer had been used to distinguish CNCP patients, so the covariates did not include cancer as one of the chronic conditions. All the covariates were from the baseline (the first-year of the panel).

3.3.2 Statistical Analysis

The statistical analysis included descriptive analysis, bi-variates analysis, and regression models. I checked the sample's baseline distribution of each measurement

and counted the incidence for developing new CNCP diagnosis and new opioid treatment. To show the correlation of new CNCP diagnosis and new opioid treatment episode with other factors, I conducted bivariate analysis over all covariates and total medical expenditure grouped by new CNCP and new opioid treatment from 2002 till 2011 data. Differences between groups were assessed with $\chi 2$ or Fisher's exact test for categorical variables, and Student t-test or Wilcoxon rank-sum test for continuous variables.

Many studies used two-part model to estimate the medical expenditure, of which the first part was a logistic regression to estimate the likelihood of have non-zero expenditure and the second part was a regression model to assess the positive expenditure. For the second part regression models, GLM with gamma distribution and log-link function was a popular option. Some studies adopted quantile regressions to fit their data better. The model specifications were decided by the data availability and features. Still, there were some disadvantages of the two-part model approach. It was hard to simultaneously interpret the coefficients estimations from the logistic regression and the second part regression. Also, for the longitudinal data, it was difficult to detect the intra-class correlations among measurements from the same study object by the GLM or the quantile regressions.

I adopted generalized linear mixed models (GLMMs) to estimate the impact of new CNCP diagnosis and new opioid treatment (separately) on annual health expenditures for the same patient adjusted for all covariates. The model specification was:

$$y_{ij} = \beta_{0ij} + \beta_1 x_{1ij} + \cdots + \beta_z x_{zij}$$

$$\beta_{0ij} = \beta_0 + u_{0j}$$

$$u_0 \sim N(0, \sigma^2_{u_0})$$

y_{ij} was the health expenditure for patient *i* at *j* time. The β s at the first equation were fixed effects and β_{0ij} at the second equation was the random intercepts. The $\sigma^2_{u_0}$ was the variance parameters to be estimated.

Since the distribution of the health expenditures were right skewed with excess of zero values and a minority of high cost patients, the GLMMs handles zero-inflation and the gamma distribution fitted the data. By tolerating correlations within a subject via the hierarchical structure, this model could account for the overdispersion in the medical expenditure, which was caused by the excess zero values. In order to capture the distribution of the random residuals, a log-link function was adopted. Moreover, the GLMMs allowed both fixed and random effects treating patient-specific intercepts and linear change with time as random effects. This approach could assess the long-term opioid treatment (the key fixed effect) on the average change in total annual medical expenditure while accounting for the dependence of within-patient repeated measures over time.

The estimation calculated 95% confidence intervals, and the difference of expenditures were tested by non-parametric tests (will add citation later). All the analyses were performed using StataSE13 (Stata Corp, College Station, Texas, 2014) *gllamm* package (Generalized Linear Latent And Mixed Models) by maximum likelihood (Sophia Rabe-Hesketh & Anders Skrondal, 2012).

3.4 Results

3.4.1 Cohort Selection Results

By using the same method as the cross-sectional analysis, I identified a total of 49,763 CNCP patients over 92,058 patients from 6 MEPS Longitudinal panels during 2000-2011 period. The new developed patients were defined as no CNCP diagnosis at the first year of the panel data, but with CNCP diagnosis at the second year of the panel data. And 27,723 patients were identified as new developed CNCP patients. Among the CNCP patients, there were 2,754 under opioid treatment, of which there were 1,072 patients with the initiation of long-term opioid treatment. The data selection steps and results were shown in Figure 4:

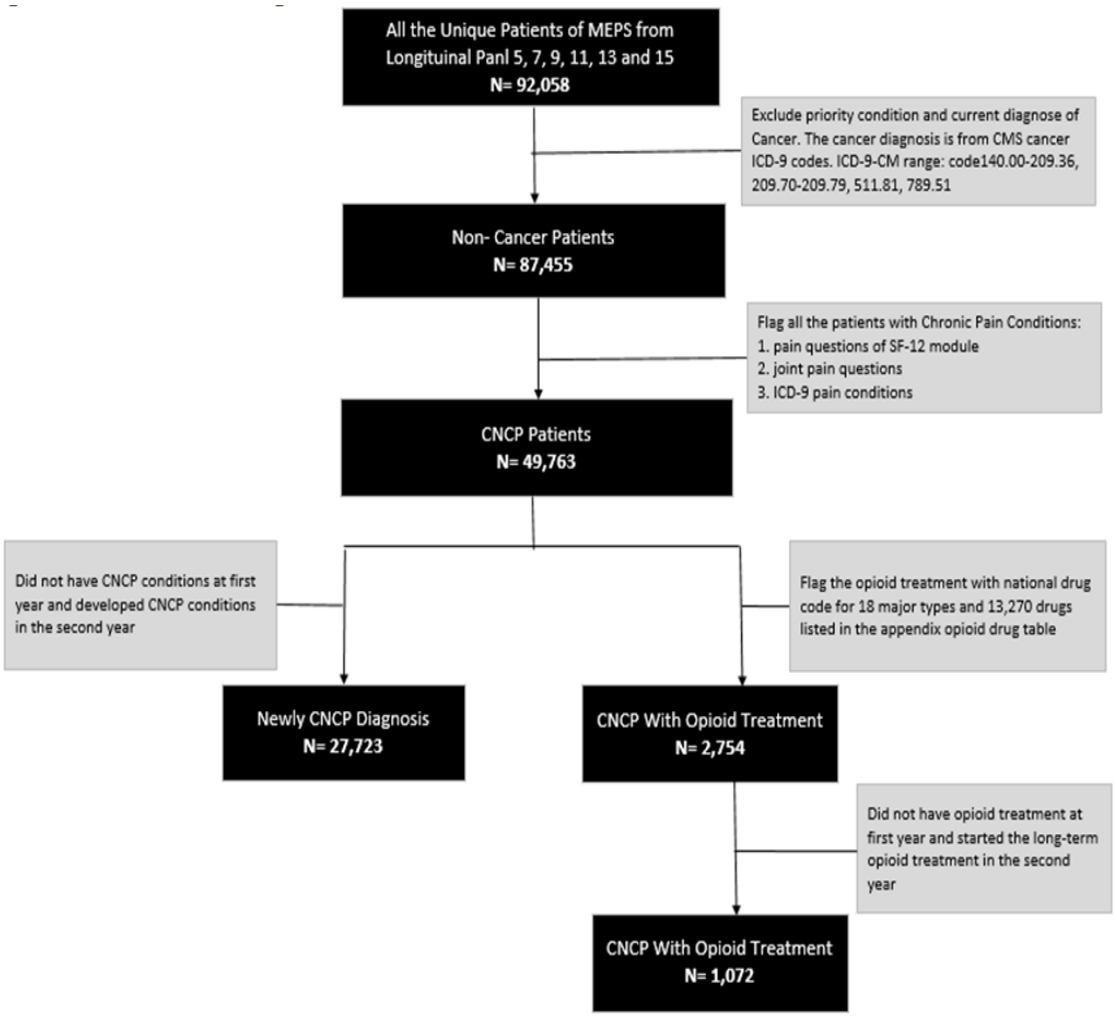

Figure 4 2000-2012 Longitudinal MEPS Cohort Selection.

3.4.2 Descriptive Analysis Results

3.4.2.1 New CNCP diagnosis as the major predictor variable

The descriptive analyses result of new CNCP patients were shown in the table 5. By applying the MEPS longitudinal weight, the 27,723 observations in the sample represented 82,174,574 non-institutional population. The average age of the sample was 49 years old, 51% were male, white individuals were the majority (65%), followed by 16% Hispanic, 12% black and 7% other races. Currently married were 51% and 49% were currently single. 63% individuals had kept private insurance, 19% public insurance, 4% uninsured, and 14% changing insurance status or unknown. Most of the individuals were in MSA (81%), 18% not in MSA, and 1% unknown. For the health conditions, the tables showed the percent of people in each BMI category and health status category, as well as the rate of high blood pressure, heart disease, stroke, emphysema, bronchitis, asthma, high cholesterol, diabetes, and arthritis.

Table 6 Descriptive Analysis of 2000-2011 New CNCP Sample. (n=27,723)

Variables	Mean Or %	S.D.
Age	49	21
Gender		
Male	51%	0.2%
Female	49%	0.2%
Race/ Ethnicity		
White	65%	0.7%
Black	12%	0.4%
Hispanic	16%	0.6%
Other	7%	0.3%
Marital Status		
Current Married	49%	0.4%

Table 6 (continued)

Variables	Mean Or %	S.D.
Insurance		
Keep Any Private Insurance	63%	0.50%
Keep Any Public Insurance	19%	0.30%
Keep Uninsured	11%	0.20%
Private shift to Public	1%	0.10%
Public shift to Private	1%	0.10%
Unknown	5%	0.00%
MSA		
Keep Yes	81%	0.20%
Keep No	18%	0.20%
Changed	1%	0.10%
BMI		
Under weight	2%	0.00%
Normal weight	37%	0.30%
Overweight	35%	0.30%
Obesity	26%	0.30%
High Blood Pressure	15%	0.00%
Heart Disease	3%	0.20%
Stroke	2%	0.10%
Emphysema	1%	0.00%
Bronchitis	3%	3.00%
Asthma	10%	0.20%
High Cholesterol	25%	0.10%
Diabetes	6%	0.10%
Arthritis	11%	3.00%
Health Status		
Excellent	22%	0.40%
Very Good	41%	0.30%
Good	29%	0.30%
Fair	7%	0.10%
Poor	1%	0.00%

There were 4% had zero health expenditure in the first year and reduced to 2% in the second year, which were statistically significant change (p=0.00). The average total annual health expenditure was $2,837 for the first year and $4,074 for the second year (p=0.00).

Table 7 Expenditure Comparison for MEPS New CNCP longitudinal Sample.

Variables	Mean Or % zero expenditures				Difference	
	1st year		2nd year		ΔMean	Δ of % $=0**
Office Visits *	$741	6%	$926	4%	$185	2%
Hospital Outpatient Visits *	$707	87%	$1,412	83%	$705	4%
Ambulatory Visits*	$111	81%	$177	77%	$66	4%
Hospital Inpatient Stays*	$1,258	95%	$2,691	90%	$1,433	5%
ED Visits *	$161	88%	$176	81%	$15	7%
Prescribed Medicines*	$608	37%	$673	26%	$65	11%
Home Health Care	$138	99%	$144	98%	$6	1%
Total Medical Expenditures	$2,837	4%	$4,074	2%	$1,237	2%

*P-value<0.05
**$=0 means zero expenditure

3.4.2.2 New Opioid treatment as the major predictor variable

The descriptive analyses result for patients started new opioid treatment were shown in the table 6. By applying the MEPS longitudinal weight, the 2,754 observations in the sample represented 4,881,281 non-institutional population. The average age of the sample was 50 years old, 41% were male, white individuals were the majority (75%), followed by 14% Hispanic, 8% black and 4% other races. Currently married were 51% and 49% were currently single. 56% individuals had kept private insurance, 33% public insurance, 4% uninsured, and 7% changing insurance status. Most of the individuals

were in MSA (84%). For the health conditions, the tables showed the percent of people in each BMI category and health status category, as well as the rate of high blood pressure, heart disease, stroke, emphysema, bronchitis, asthma, high cholesterol, diabetes, and arthritis.

Table 8 Descriptive Analysis of 2000-2011 New Opioid Treatment Sample. (n=2,754)

Variables	Mean Or %	S.D.
Age	50	17
Gender	41%	3.0%
Male	59%	0.1%
Female		
Race/ Ethnicity		
White	75%	2.0%
Black	14%	2.0%
Hispanic	8%	1.0%
Other	4%	1.0%
Marital Status		
Current Married	51%	0.4%
Current Single	49%	3.0%
Insurance		
Keep Any Private Insurance	56%	3.0%
Keep Any Public Insurance	33%	3.0%
Keep Uninsured	4%	2.0%
Private shift to Public	4%	0.3%
Public shift to Private	3%	1.0%
MSA	84%	3.0%
BMI		
Under weight	0.4%	2.0%
Normal weight	27%	3.0%
Overweight	32%	3.0%
Obesity	41%	3.0%
High Blood Pressure	15%	0.0%
Heart Disease	5%	4.0%
Stroke	4%	1.0%

Table 8 (continued)

Variables	Mean or %	S.D.
Emphysema	3%	2.0%
Bronchitis	2%	2.0%
Asthma	22%	3.0%
High Cholesterol	40%	0.4%
Diabetes	15%	0.2%
Arthritis	49%	0.30%
Health Status		
Excellent	7%	0.00%
Very Good	28%	0.10%
Good	29%	0.30%
Fair	24%	0.30%
Poor	11%	0.20%

There were 4% had zero health expenditure in the first year and reduced to 0% in the second year, which were statistically significant change (p=0.00). The average total annual health expenditure was $7,970 for the first year and $13,569 for the second year (p=0.00).

Table 9 Expenditure Comparison for MEPS New Opioid Treatment Sample.

Variables	Mean or % zero expenditures				Difference	
	1st year		2nd year		ΔMean	Δ of % $=0
Office Visits *	$1,729	8%	$2,722	5%	$993	3%
Hospital Outpatient Visits *	$1,644	65%	$5,820	57%	$4,176	8%
Ambulatory Visits*	$202	63%	$516	55%	$314	8%
Hospital Inpatient Stays*	$1,258	86%	$2,691	72%	$1,433	14%
ED Visits *	$394	70%	$421	61%	$27	7%
Prescribed Medicines*	$1,861	7%	$2,064	0%	$203	7%
Home Health Care	$280	93%	$144	92%	$-136	1%
Total Medical Expenditures	$7,970	4%	$13,569	0%	$5,599	4%

*P-value<0.05

3.4.3 Regression Model Results

3.4.3.1 New CNCP diagnosis as the major predictor variable

The GLMMs regression model results for new CNCP patients 2nd year health expenditures were shown in the table 10. The mixed-effects regression showed the estimated health expenditure for new CNCP patients were $2,590 increase for the second year, after adjusted for demographic, SES, geographic, and health conditions. One-year age increase were associated with $80 increase of health expenditure increase. The individuals with private insurance $247 or with public insurance $430 had higher health expenditure than the people who uninsured or changing insurance status. MSA associated with $135 health expenditure increase. The high blood pressure ($359 higher) and heart disease ($239 higher) also related to higher health expenditure increase. Compared to excellent health status, other health status categories increase the health expenditure, which were shown in the table 10. The level 1 variance is 0.48 with 0.0001 standard deviation.

Table 10 GLMMs regression of Health Expenditure for New CNCP.

Variables	Coef.	Std. Err.	P>z	[95%	C.I.]
New CNCP*	2,590	155	0.00	2279	2901
Age*	80	2	0.00	80	82
Male	159	10	0.79	159	161
White	Ref				
Black	-56	-4	0.39	-56	-54
Hispanic*	-183	-13	0.00	-183	-182
Other	-144	-16	0.12	-144	-143
Current Married	Ref				
Current Single	88	5	0.08	88	90
Keep Any Private Insurance	534	150	0.00	533	536
Keep Any Public Insurance*	430	112	0.01	429	432
Private shift to Public	247	89	0.33	246	249
Public shift to Private	518	249	0.09	517	520
MSA*	135	11	0.03	135	137
Under weight	Ref				
Normal weight	175	39	0.37	175	176
Overweight	231	46	0.23	231	232
Obesity	207	43	0.29	207	208
High Blood Pressure*	359	54	0.00	359	361
Heart Disease*	239	22	0.00	239	241
Stroke	159	19	0.06	159	161
Emphysema	151	26	0.22	151	153
Bronchitis	56	10	0.95	56	57
Asthma	159	17	0.05	159	161
High Cholesterol	56	4	0.31	56	58
Diabetes*	391	43	0.00	391	394
Arthritis*	143	11	0.01	143	145
Health Status Excellent	Ref				
Health Status Very Good*	454	104	0.00	454	456
Health Status Good*	677	176	0.00	676	680
Health Status Fair*	573	235	0.00	572	577
Health Status Poor*	3,132	2161	0.00	3131	3138

*P-value<0.05

3.4.3.2 New Opioid treatment as the major predictor variable

I also did the GLMMs model for the estimation of impact of new opioid treatment on health expenditures, which was reported in the table 11. The regression showed the estimated health expenditure for starting new opioid treatment patients were $5,468 increase for the second year, after adjusted for demographic, SES, geographic, and health conditions. One-year age increase were associated with $55 health expenditure increase. The individuals with private insurance ($476 higher) or with public insurance ($394 higher) had higher health expenditure than the people who uninsured or changing insurance status. MSA associated with $1,039 health expenditure. Compared to underweight, the normal weight was $2,078 less. The high blood pressure ($3,251 higher), heart disease ($1,203 higher) and ($2,187 higher) also related to higher health expenditure increase. Compared to excellent health status, other health status categories increase the health expenditure, which were shown in the table 11. The level 1 variance is 0.55 with 0.0002 standard deviation.

Table 11 GLMMs regression of Health Expenditure for New Opioid Treatment.

Variables	Coef.	S.D.	P>z	[95%	C.I.]
New Opioid*	5,468	2,078	0.01	1312	9,624
Age*	55	0	0.00	55	57
Male	109	8	0.68	109	111
White	Ref				
Black	-164	-15	0.73	-164	-162
Hispanic	820	66	0.08	820	822
Other	437	70	0.60	437	439
Current Married	Ref				
Current Single	273	19	0.52	273	275
Keep Any Private Insurance*	476	171	0.00	475	478
Keep Any Public Insurance*	394	138	0.00	393	396
Private shift to Public*	328	171	0.07	327	330
Public shift to Private*	1,531	1,608	0.00	1529	1,534
MSA*	1,039	94	0.03	1039	1,041
Under weight	Ref				
Normal weight*	-2,078	-416	0.14	-2078	-2,077
Overweight	-2,679	-429	0.03	-2680	-2,679
Obesity	-2,351	-423	0.08	-2352	-2,351
High Blood Pressure*	3,281	558	0.01	3280	3,283
Heart Disease*	1,203	120	0.02	1203	1,205
Stroke	12	2	0.07	12	14
Emphysema	1,094	208	0.27	1093	1,095
Bronchitis	2,734	1,039	0.06	2733	2,736
Asthma	711	78	0.21	711	713
High Cholesterol	219	-15	0.62	-219	-217
Diabetes*	2,187	262	0.00	2187	2,190
Arthritis	492	39	0.24	492	494
Health Status Excellent	Ref				
Health Status Very Good*	2,515	830	0.01	2515	2,518
Health Status Good *	492	182	0.00	491	495
Health Status Fair*	10,936	5,468	0.00	10935	10,939
Health Status Poor*	16,404	12,139	0.00	16403	16,409

*P-value<0.05

3.5 Discussion and Limitations

This chapter confirmed the assumptions of 1) new CNCP diagnosis associated with higher health expenditure, 2) starting new episode of opioid treatment increased health expenditure. The outcomes validated the estimations in cross-sectional analysis.

Base on the 2000-2011 MEPS panel data, this chapter tracked the impact of new CNCP diagnosis and new opioid treatment on healthcare expenditure by the longitudinal model. The unadjusted average total expenditure increased $1,237 in 2nd year after new CNCP diagnosis and increased $5,599 in 2nd year after starting new opioid treatment.

For adjusted estimations from the GLMMs models, mean yearly total health expenditure was $2,590 higher for new CNCP diagnosed patients compared to non-CNCP diagnosis patients, and $5,468 higher for patients starting new opioid treatment after adjusted for demographic, SES, and health conditions. The GLMMs regression model combined covariates' impact on expenditure with opioid treatment as the major predictor. Also, the model handled zero-inflation and skewness of the expenditure, as well as addressed the intra-class correlations among measurements from the same study object repeatedly at different time points.

The results highlighted the economic burden caused by development of CNCP conditions, as well as the incremental cost of opioid treatment. Moreover, the estimation in this chapter align with other studies (Maeng et al., 2017; Smith et al., 2013). While the difference of per capital average annual total health expenditure before and after opioid treatment in longitudinal analysis was not as dramatic as the cross-sectional analysis results, it still increased the whole society's economic burden and showed significant

cost for the whole health care system. The outcomes showed necessity to better manage CNCP condition in a more efficient and effective way. The stakeholders could use this estimation to evaluate alternative treatments and to make decision based on the cost and effectiveness.

Even though the analysis gave insights about the health expenditure change associated with CNCP condition development, and initiation of new opioid treatment, it was important to understand the limitation of the analysis. One limitation was that the model was tracking the health expenditure change when new CNCP condition happened or new episode opioid started, which were consecutive events. But the model did not reveal the causal relationship between the independent variables and the dependent variable. Also, there were only two years record for each panel. The results could be more informative if the cohort could be tracked longer to check long-term impact on health expenditure. Another limitation was this study did not distinguish the level of pain in the model, which could give more insights of the major expenditure driven factors.

3.6 Conclusion

This chapter found new CNCP conditions associated with $2,590 higher annual total health expenditure, and the initiation of new episode of long-term opioid treatment increased $5,468 higher annual total health expenditure. This pattern was consistent with cross-sectional analysis results. By applying the longitudinal weight, the results showed national level impact of the high cost of CNCP conditions and opioid treatment, which emphasized the need for more cost-effective management for CNCP patients.

CHAPTER 4. BLUE CROSS/BLUE SHIELD OF TEXAS ANALYSIS

4.1 Introduction

As noted previously, the MEPS data provided many advantages for analyzing the research questions addressed in this study, but the MEPS data also had potentially important limitations, mainly related to self-reporting of key variables by survey respondents. To determine if the results from the MEPS data were substantially affected by these limitations, I replicated the previously reported MEPS analyses using claims data from Blue Cross/Blue Shield of Texas (BCBSTX).

The analysis in this chapter included: cross-sectional model to estimate the difference in health expenditures and adverse events (ER visits) between CNCP long-term opioid treatment group vs. CNCP non-opioid treatment group; longitudinal models to compare the health expenditure before and after CNCP diagnosis and to track the health expenditure change after initiation of the long-term opioid treatment for CNCP patients. There were three major research questions in the longitudinal part: 1) Are there any changes in medical expenditures and/or specific types of medical resources use (e.g., ED visits) associated with the onset of CNCP; and 2) How much change in total medical spending and/or specific types of medical resources use do we see after initiation of long-term opioid treatment for CNCP patients, as compared to non-opioid CNCP patients. 3) How much change in total medical spending and/or specific types of medical resources use do we see after new diagnosis of CNCP, as compared to before diagnosis of CNCP conditions. The model specifications were similar to the previous chapters,

which included cross-sectional mass-univariates analysis, the GLM regressions, and the longitudinal regression models. Due to the limitation of data, those models only adjusted for the basic demographic information, which are age and gender. The data were from CY2008-CY2012 BCBSTX.

4.2 Data

Unlike the self-reported data in MEPS, the BCBSTX claims provided an option to completely capture all medical care services with claims processed by BCBSTX. There were several benefits of using the BCBSTX claims data for the study aims. First, the large number of claim records would provide an adequate sample to estimate the prevalent or incident of CNCP conditions. Also, the dataset included 5 years' BCBSTX claims, which enabled the longitudinal analysis. Second, the BCBSTX medical claims data contained the ICD-9 diagnosis codes and HCPCS/CPT codes which were needed to identify specific individuals in the database meeting the case-finding definitions for CNCP conditions, and the pharmacy claims contained National Drug Code (NDC) codes which were needed to identify all the long-term opioid treatment. Finally, the BCBCTX database included expenditure (payment) information, which was necessary to estimate the incremental expenses associated with incident CNCP conditions and differences in medical costs between opioid and non-opioid treatment groups. While some medical care use may be missed using claims data, these errors generally have a limited impact on measurement of total medical care expenditures (Wolinsky et al. 2007).

The cross-sectional analysis compared the expenditure difference for CNCP patients between the opioid treatment group and non-opioid treatment group. This analysis used calendar year 2011 claims data to match the MEPS cross-sectional analysis, with the sample of CNCP patients selected based on the presence of claims history during 2011 consistent with the case-finding definitions for CNCP conditions used in the study. The claims include both professional and facility claims.

The longitudinal analysis focused on the change in medical expenditures associated with the onset of CNCP and the initiation of new opioid treatment, I also used all claims data (professional and facility claims) for CY2008 through CY2012 to identify new cases of CNCP for CY2009 and each calendar year thereafter (defined as the presence of diagnosis codes identifying CNCP following at least 1 year of claims without CNCP codes). Once the date of onset of new CNCP is established for each patient, for each new CNCP patient I calculated total medical expenditures (and specific resource use counts) for 1 year prior to the patient's CNCP onset date and for at least 1-year post-CNCP onset, which was up to 3 years of follow-up.

The study used a similar approach to identify new episodes of long-term opioid use in the data. A new episode of long-term opioid treatment was defined as beginning on the first date of an opioid prescription for a CNCP patient (after CNCP onset date), following a period of at least 6 months without any opioid prescriptions, resulting in at least 90 days supplied for one or more opioids over a subsequent 180-day period. The study restricted the final sample of CNCP patients employed in the longitudinal analysis

to patients with continuous eligibility over both calendar years (2008-2009, 2009-2010, 2010-2011, 2011-2012).

4.3 Methods

The analyses included three parts: 1) descriptive analysis, 2) cross-sectional analysis, 3) longitudinal analysis. For the descriptive analyses, I described the basic features of the CNCP sample by providing summaries about the sample and the measures. I then used univariate analysis to estimate the demographic and clinical characteristics of participants as proportions for categorical variables and means with standard deviations (SD) for continuous variables. Finally, I did a histogram chart to show the distribution of the health expenditures for CNCP patients with and without long-term opioid treatment at 2011.

4.3.1 Method for the Cross-Sectional Analysis

To address hypothesis 1 that the opioid treatment group will have higher total medical expenditures than non-opioid patient, total medical expenditures are measured by the summing the variable "total paid amount" over a given year. By using the drug claim file, I flagged the opioid treatment patients if they had filled opioid prescriptions list which included 13,270 drugs (NIDA, 2018) in appendix 1. The filled prescription was defined as non-zero payment and unit. To test for differences in expenditures between the opioid and non-opioid treated CNCP groups, I used a t-test and define statistical significance at the 5 percent significance level.

To estimate overall expenditures for the CNCP patients with and without opioid treatment when adjusted for demographic and socioeconomic status, I adopted a linear regression and a log-link Gamma regression model using patient-level characteristics as covariates. Similarly, I used a logistic or count-based regression model to assess the impact of opioid or non-opioid pain treatment on ED use among patients with CNCP.

For hypothesis 2, which supposed the opioid treatment group would have more ER visits than non-opioid patients, I defined the ER visit by Current Procedural Terminology (CPT) / Healthcare Common Procedure Coding System (HCPCS) Code in the range of “99281" to "99285", as well as the Revenue code "0450","0451","0452","0456","0459" and "0981 ". I conducted a t-test to show the unadjusted difference of the average of total count of ER visits between the opioid and non-opioid group. I also performed a logistic regression, using ER (Yes=1, No=0) as the outcome variable and opioid treatment as the predicted variable, and adjusted for patient-level demographic and (geo-coded proxy measures of) socioeconomic characteristics to show the odds ratio of ER events for the opioid and non-opioid group.

For the cross-sectional analysis, the annual overall medical expenditures across CNCP and non-CNCP groups at baseline were compared using linear regression models including long-term opioid treatment as the independent variable and annual total paid medical expenditures as a dependent variable adjusting for sociodemographic variables. The construction of the regression models depends also upon the availability of data. The model specification for general linear repeated measure models (GLM) with log link is

$$E[y|x] = f(x'\beta) = \exp(x'\beta)\, In(E[y|x]) = x'\beta$$

and gamma distribution

$$y \sim Var(y|x) \approx (E[y \mid x])^{\lambda}$$

to test the differences in medical expenditures across CNCP and non-CNCP groups at 2011, This model connected the linear predictor and the mean of the distribution function by allowing dependent variables had arbitrary error distribution, which fitted CNCP sample better than the ordinary linear regression (OLS) model (Nelder JWedderburn, 1972). The GLM estimator with gamma distribution and a log-link function relaxed the assumption that the error distribution must follow a normal distribution and solved heteroskedasticity issues. I conduced several diagnostic tests for modeling fitting. I used modified Park test for the GLM family. To be more specific, the Gamma distribution suited to dealing with heteroskedasticity in non-negative data. Manning and Mullahy recommended a modified Park test to confirm the choice of distribution family of the regression mode as the correct specification among different GLMs (Manning & Mullahy, 2001). The Pearson correlation test was for checking systematic bias in fit on raw scale. After regression, Hosmer-Lemeshow tests were performed to check if the link functions fit the data well, which tested first divide the observations into 10 identical sized clusters based on predicted values, and then use F-test to check if the mean residuals are equal among the 10 clusters. If null hypothesis was not rejected, the model shows goodness-of-fit (Hosmer & Lemeshow, 2000). And the Pregibon link test checked linearity of response on scale of estimation.

4.3.2 Method for the Longitudinal Analysis

To answer the research questions, the longitudinal analysis addressed the following hypotheses: H1) the onset of new CNCP diagnosis would increase total medical expenditures, and H2) among CNCP patients the initiation of a new episode of long-term opioid prescription use will increase total medical expenses for CNCP patients. To test the hypotheses, I adopted the GLMMs model, which allowed both fixed and random effects treating patient-specific intercepts and linear change with time as random effects. This approach allowed me to assess the new CNCP diagnosis or the new episode of long-term opioid treatment (the key fixed effects) on the average change in total annual medical expenditure while accounting for the dependence of within-patient repeated measures over time. The model specification was:

$$y_{ij} = \beta_{0ij} + \beta_1 x_{1ij} + \cdots + \beta_z x_{zij}$$

$$\beta_{0ij} = \beta_0 + u_{0j}$$

$$u_0 \sim N(0, \sigma^2_{u_0})$$

The y_{ij} was the health expenditure for patient *i* at *j* time.

The β s at the first equation were fixed effects and β_{0ij} at the second equation was the random intercepts.

The $\sigma^2_{u_0}$ was the variance petameters to be estimated.

Since the distribution of the health expenditures were right skewed with excess of zero values and a minority of high cost patients, the GLMMs handles zero-inflation and the gamma distribution fitted the data.

By tolerating correlations within a subject via the hierarchical structure, this model could account for the overdispersion in the medical expenditure, which was caused by the excess zero values. In order to capture the distribution of the random residuals, a log-link function was adopted. Moreover, the GLMMs allowed both fixed and random effects treating patient-specific intercepts and linear change with time as random effects. This approach could assess the long-term opioid treatment (the key fixed effect) on the average change in total annual medical expenditure while accounting for the dependence of within-patient repeated measures over time.

Since there were not many covariates in the BCBSTX data, the GLMMs models only included age (continuous), sex (male and female), race (white, black, Hispanic and other), marital status (married or not), income (average household income by ZIP Code), Charlson comorbidity index (no comorbidity, low comorbidity, and high comorbidity), and initiation of new-opioid treatment or new-diagnosis of CNCP.

The estimation calculated 95% confidence intervals, and the difference of expenditures were tested by non-parametric tests. All the analyses were performed using StataSE13 (Stata Corp, College Station, Texas, 2014) *gllamm* package (Generalized Linear Latent and Mixed Models) by maximum likelihood (Rabe-Hesketh & Skrondal, 2012).

4.4 Results

4.4.1 Results for the Cross-Sectional Analysis

There were 2,623,290 unique patients from 2008 to 2012 in BCBSTX. By applying the CNCP flag, I identified 498,800 patients with CNCP conditions in 2011, and 14% of those patients had long term opioid treatment. The yearly prevalence for CNCP patients counts and patients with long opioid treatment are shown in table 10. The yearly CNCP was increasing from 2008 to 2012 in both absolute count and percent over overall patients. The number of CNCP patients with opioid treatment grew from 2008-2012, but the rate of patients under opioid treatment over all CNCP patients remained consistent (14%) during those years.

Table 12 Sample size for BCBSTX Cross-Sectional Analysis.

Year	All unique patients	CNCP Patients		CNCP with Long-term Opioid patients	
2008	1,629,367	369,723	22%	48,818	13%
2009	1,763,210	419,877	24%	58,296	14%
2010	1,835,525	457,696	25%	66,265	14%
2011	1,882,601	498,800	26%	68,419	14%
2012	1,814,814	493,513	27%	70,321	14%

In the cross-sectional part, the descriptive analysis showed the percent or mean of each covariate, dependent and independent variable for 2011 CNCP sample. Among all the CNCP patients, 14% received long-term opioid treatment. Males were only 37% of the CNCP sample. The average age was 47. The annual average total health expenditure was $6,650.

Table 13 Descriptive Results for 2011 BCBSTX Cross-sectional Analysis.

Variables	Opioid Treated CNCP Patients (n=68,419)		Non-Opioid Treated CNCP Patients (n=430,381)		Overall CNCP Patients (n=498,800)	
	n	%	n	%	n	%
Charlson Comorbidity Index						
0: no comorbidity	41,023	60%	296,677	69%	337,700	68%
1: low comorbidity	17,692	26%	91,433	21%	109,125	22%
2: high comorbidity	9,704	14%	42,271	10%	51,975	10%
Male	27,935	41%	157,769	37%	185,704	37%
	Mean	S. D.	Mean	S. D.	Mean	S. D.
Age	47	12	47	14	47	14
Income (Median income of each zip)	59,843	23,786	59,919	24,803	59,909	24,666
Total Annual Payment	14,582	35,014	5,389	20,327	6,650	23,044

To show the distribution of annual health care expenditure, I created two histogram charts: one is for all the CNCP patients' expenditure (figure 5), and the other one included up to the 95 percentiles expenditures (figure 6). The reason of having two charts was the long right-hand tail of the expenditure, which represent some outlies over one million dollars. In the figure 5 and 6, the annual total health care expenditure was left side skewed and the majority (>50%) CNCP patients had less than $10,000 annual health expenditure.

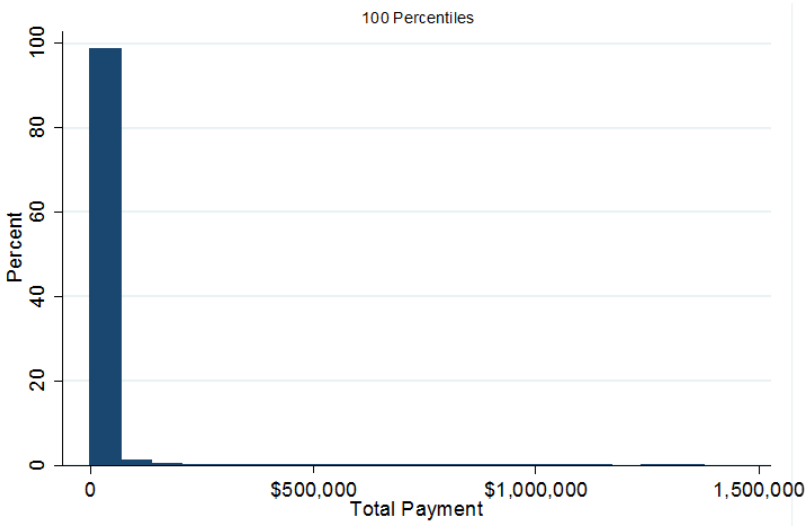

Figure 5 Histogram for 2011 All CNCP Patients Annual Healthcare Expenditure.

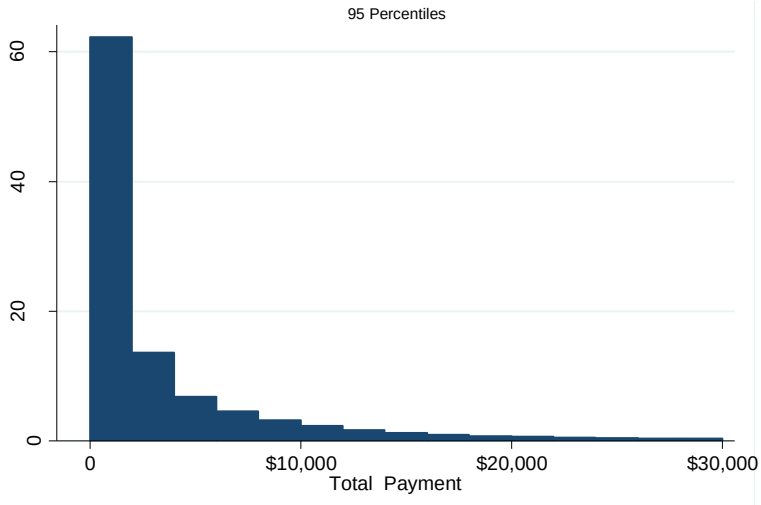

Figure 6 Histogram for 2011 CNCP Patients Annual Healthcare 95 Percentiles Expenditure.

I ran OLS and GLM regression models for the cross-sectional analysis; table 14 showed the impact of opioid treatment on annual total health expenditure after adjusting for the demographic covariates. According to the coefficient's estimations, the opioid

treatment group had $21,681 higher health expenditure than non-opioid treatment in the OLS model, and 2.65 times higher in GLM model after adjusting for gender and age.

Table 14 Regression results for cross-sectional analysis for 2011 BCBSTX.

Variables	OLS			GLM		
	Coef	P-value	95% C.I.	Exp (Coef)	P-value	95% C.I.
Opioid	8,103	0.00	[7,923, 8,283]	2.60	0.00	[2.54, 2.65]
Male	167	0.00	[39, 295]	1.02	0.00	[1.00, 1.04]
Age	-19	0.00	[-24, -14]	1.00	0.00	[1.00, 1.00]
Comorbidity	Reference group Comorbidity index is 0					
Low	3,933	0.00	[3,778, 4088]	2.09	0.00	[2.05, 2.13]
High	20,907	0.00	[20,692, 21,122]	6.64	0.00	[6.48, 6.81]
Income	.02	0.00	[.01, .02]	1.00	0.00	[1.00, 1.00]
Cons	4472	0.00	[2,114, 2,662]	8.4	0.00	[8.37, 8.43]

4.4.2 Results for the Longitudinal Analysis

For the longitudinal analysis sample, the final cohort count was reported in the table 16. Around 62% patients had 2-years continuous enrollment and 28% of those patients had CNCP conditions in both years. The new diagnosed CNCP conditions were around 22% of 2-years continuous enrolled patients. The initiation of new opioid episode was around 2% among patients with CNCP conditions in both years.

Table 15 Sample Selection for BCBSTX Data.

Year	Continuously enrolled 2 years	CNCP in both years	New diagnosed CNCP		CNCP patient initiation of new opioid episode	
	#	#	#	% *	#	% **
2008-2009	741,520	137,828	166,198	22%	3,321	2%
2009-2010	824,641	164,445	176,323	21%	3,979	2%
2010-2011	874,588	182,611	188,261	22%	4,209	2%
2011-2012	866,774	186,475	184,669	21%	4,432	2%

* Denominator: two-year continuously enrolled patients
** Denominator: CNCP in both years

The descriptive analysis for new diagnosis of CNCP conditions (table 17) showed a statistically significant difference in annual health expenditure change, gender, comorbidity and age between new diagnosed CNCP group and non-new diagnosed CNCP group. The new CNCP group was slightly older, and female with higher Charlson comorbidity score. There was $ 6,542 expenditure increase for the new CNCP group and $509 decrease for non-new CNCP.

Table 16 Descriptive Analysis of New Diagnosed CNCP.

Variables	New CNCP (n=715,451)		Non-new CNCP* (n=5,459,586)		Overall (n=6,175,037)	
	n	%	n	%	n	%
Male*	262,195	37%	2,148,692	39%	2,410,887	39%
Comorbidity*						
0 no comorbidity	372,586	69%	2,689,692	74%	3,062,278	73%
1 low comorbidity	113,437	21%	648,647	18%	762,084	18%
2 high comorbidity	53,105	10%	298,520	8%	10%	9%
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Age*	46	13.59	45	13.72	46	13.71
Income (by zip)	59,725	29.52	59,630	10.64	59,641	10.01
Difference of Expenditures*	6,542	26.51	-509	12.58	308	11.43

* (Prob>F) <0.05

**Non-new CNCP group include patients no CNCP conditions in both years, CNCP conditions in both years, with CNCP in the first year and no CNCP in the second years

The descriptive analysis for CNCP patients with new opioid episode (table 18) showed a statistically significant difference of gender, age, and Charlson comorbidity score. The new opioid treatment patients were more like to be males, higher comorbidity scores, and slightly younger age. There was $7,841 increase of annual health expenditure for new opioid group. The increase of annual health expenditure was $7,679 higher for the new opioid group than the non-new opioid group.

Table 17 Descriptive Analysis of CNCP Patients Starting New Episode of Opioid Treatment.

Variables	**New Opioid** (n=15,941)		**Non-new opioid** (n=655,418)		**Overall**** (n=671,359)	
	n	%	n	%	n	%
Male*	5,658	35%	219,308	33%	224,966	34%
Comorbidity*						
0 no comorbidity	6,698	56%	301,380	61%	308,078	61%
1 low comorbidity	3,432	29%	126,420	26%	129,852	26%
2 high comorbidity	1,832	15%	67,152	14%	68,984	14%
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Age*	49	13	50	14	50	14
Income (by zip)	58,994	191	58,896	30	58,898	30
Difference of Expenditures*	7,841	292	162	35	344	35

*: (Prob>F) <0.05

**All the patients were CNCP patients who had two-years continuous CNCP conditions

The GLMMs regression model estimated the change of medical expenditures for new developed CNCP patients. For the goodness of fit, the R^2 between was 0.15. If using these estimates to predict the within model, the R^2 was 0.08. If using these estimates to fit the overall data, the R^2 was 0.11. The F statistic tests that all coefficients on the regressors are jointly zero, and this model was significant (Prob>F=0.00). The level 1 variance is 0.46 (S.D. 0.0001). After adjusting for gender, age, comorbidity, income, new diagnosis of CNCP conditions was associated with $2,567 more increase of annual medical expenditures than non-new diagnosed CNCP patients. This study also used a GLMMs regression model to estimate the annual medical expenditures for established CNCP patients with initiation of a new episode of long-term opioid treatment.

For the goodness of fit, the R^2 between was 0.15. If using these estimates to predict the within model, the R^2 was 0.05. If using these estimates to fit the overall data, the R^2 was 0.12. The F statistic tested that all coefficients on the regressors are jointly zero, and this model was significant (Prob>F=0.00). I also did the Hausman random effects tests and the results showed there were no random effects. After adjusting for gender, age, and age interaction, initiation of new opioid treatment was associated with $6,625 increase of total average annual medical expenditures than non-new opioid treatment CNCP patients. Male was omitted due to the collinearity since it did not vary within person.

Table 18 GLMMs Results for Newly CNCP Diagnosis Patients and New Start of the Opioid Episode.

Variables	**New CNCP Model**			**New Opioid Model**		
	Coef.	P-value	95% C.I.	Coef.	P-value	95% C.I.
New CNCP	2,567	0.00	[2,305, 2,413]			
New Opioid				6,625	0.00	[5,409, 6,890]
Male	408	0.03	[-1,707, 2,522]	-1,507	0.81	[-13,919, 10,906]
Age	49	0.03	[5, 94]	-381	0.04	[-752, -10]
Comorbidity	Ref			Ref		
0 no	3,701	0.00	[3,634, 3,767]	4,486	0.00	[4,157, 4,815]
1 low	15,110	0.00	[15,003, 15,219]	14,396	0.00	[13,903, 14,889]
2 high						
Income (by zip)	0.00	0.94	[-0.003, 0.003]	-0.01	0.26	[-0.03, 0.01]
Cons	-258	0.71	[-1,623, 1,107]	22,872	0.00	[11,910, 33,833]

4.4.3 Results for the Emergency Department Visits

For the emergency department visits, there were 24% patients had ED visit yearly for the long-term opioid CNCP group, and 15% for the non-opioid group. The opioid group is 9% higher than the non-opioid group (Pr>t=0.00). For the patients with ED, the average yearly total ED visit count for long-term opioid CNCP patients were 3 and for non-opioid treatment were 2 (Pr>t=0.00).

The study also compared the count change (increase or decrease) of yearly ED visits before and after the new CNCP diagnosis. There was 0.28 increase for patients with new CNCP diagnosis and 0.07 decrease for patients who did not have new CNCP diagnosis (Pr>t=0.00).

In addition, the study also checked the count difference of yearly ED visits before and after the initiation of new opioid episode. There was 0.28 increase for patients started new long-term opioid treatment and 0.02 decrease for patients did not have long-term opioid treatment (Pr>t=0.00).

4.5 Discussion and Limitations

Base on the five-year BCBSTX data, this chapter tested same hypotheses as the MEPS analysis to estimate the impact of opioid treatment on healthcare expenditure. Both the cross-sectional and the longitudinal models showed significant higher cost for the opioid treatment than the non-opioid treatment CNCP patient group. In the cross-sectional analysis, the adjusted mean of 2011 annual health expenditure was $8,103 higher for opioid group than non-opioid group in the OLS model. I also adopted the

GLM repeated measure regression model with gamma distribution to better fit the skew of expenditure data. Combined covariates' impact on expenditure with opioid treatment as the major predictor, the GLM repeated measure model showed the opioid group had 2.65 times of annual expenditure compared to non-opioid treatment group, which was close to MEPS estimation. The MEPS estimated mean health expenditure was 3 times higher for the opioid treatment group compared to non-opioid treatment group after matching for demographic, SES, and health conditions.

The longitudinal FE model showed the initiation of new opioid episode was $6,625 more increase than the non-new opioid episode after adjusting for age, gender, comorbidity and income. The difference of expenditure change was relatively smaller between new diagnosis of CNCP conditions and non-new CNCP conditions, which were $2,567. This estimation reveled the CNCP condition did not drive health expenditure as much as the new initiations of opioid treatment. The opioid treatment was the major factor associated with the higher health expenditure.

I also compared the count of ER visits for opioid treatment and non-opioid treatment group to better understand the difference of health utilization and adverse events associated with opioid treatment. The outcome showed statistically significant higher ER visits for opioid treatment group. Also, there was increase of ER visits after the new CNCP treatment or the initiation of new opioid treatment.

All the model showed goodness of fit. The results were consistent with MEPS outcomes and other studies' estimations. The longitudinal analysis eliminated various background variables that could affect data outcomes and the outcomes were robust.

4.5.1 Limitation

There was no previous analysis that used both national survey data and private insurance claims data to compare the overall annual health expenditures between long term opioid treatment group and non-opioid treatment group for CNCP patients. The finding showed similar difference for these two groups in either cross-sectional or longitudinal models. However, there were some limitations. First, the BCBTX data was insurance claims administration data, which only captured the claims activities and basic demographic information. There was limited social economic status variables about their members, as well as no self-reported health outcomes. In order to adjust for comprehensive potential cofounders, I linked the members' residential ZIP Code to censor data to get the median income. Also, I calculated the Charlson Comorbidity score to capture the health status of each member. Even though the covariates adjustment was not as inclusive as the MEPS analysis, the BCBSTX analysis already adjusted for all the possible covariates. The consistent estimation across different models showed the robustness of the estimations.

Another limitation was BCBSTX data only compared the total health expenditure. The MEPS analysis did compare the health expenditure in several different services' bucket, such as ER, inpatient, outpatients, office visits and so on. The data structure was different and the BCBSTX data did not have the variable or grouper to distinguish the expenditure for different services bucked. Although the outcomes showed the opioid treatment related to much higher health expenditure than the new CNCP diagnosis, it did not deep dive where those differences came from: were they caused by

adverse-effect of opioid treatment or were the utilization of a specific service bucket systematically different for opioid and non-opioid patients. But the comparison of using ER visits in BCBSTX analysis gave some clues that there were increase of adverse events which might contributed to the rise of the expenditure.

Additionally, this analysis only used Texas data, which might have some regional bias. But the outcomes were close to the national MEPS data, which proved the Texas data were sufficient.

4.5.2 Conclusion

This chapter replicated the MEPS cross-sectional and the longitudinal analysis in the five-year BCBSTX claims data. The estimation aligned with the MEPS outcomes, which showed the around 3 times higher health expenditure for CNCP patients with opioid treatment than without opioid treatment.

Although there are some limitations of this analysis, the outcomes give policymakers, payers, physicians, and CNCP patients insights about potential expenditure difference with and without the opioid treatment. Different from other one data sources study, this study analyzed both private insurance claims data and national survey data, which enhanced the validity and reliability of the outcomes.

Policymakers could use this estimation to assess the social cost for the opioid treatment and accordingly make change of the opioid management. Payers could use this outcome to adjust the reimbursement. Physicians could share this information with patients to help patient deciding on an appropriate CNCP management strategy. My

results underscore the high cost of opioid treatment to the health care system and highlight the need for cost-effective CNCP treatments.

CHAPTER 5. CONCLUSION

This study investigated the annual health expenditure difference between long-term opioid treated CNCP patients and non-opioid treatment CNCP patients in cross-sectional analyses controlling for demographic, SES and clinical characteristics. The study also compared the change of medical expenditures associated with the development of new CNCP condition and the initiation of new long-term opioid treatment episode. The analysis based on two types of data: self-reported national survey panel data (MEPS) and regional private insurance administration (Texas Blue Cross Blue Shield) claims data. The outcomes had been cross-validated from different data sources and different research designs (cross-sectional setting and the longitudinal setting). The findings demonstrated the hypotheses that CNCP condition and new opioid treatment were statistical significantly associated with higher total medical expenditure with and without risk adjustment across different data and models. Additionally, the emergency department visits were higher for CNCP patients and patients under opioid treatment.

5.1 Results

To be more specific, the estimation results from different data and different models were summarized in table 19, which showed the opioid related health expenditure difference (cross-sectional) or change (longitudinal). In the cross-sectional analysis, the difference of annual health expenditure was $23,413 for MEPS and was

$9,193 for BCBSTX in the descriptive analysis, and after adjusted for demographic, SES, comorbidity and health status, the OLS model showed opioid group was $8,103 higher than non-opioid group in BCBSTX model. And the GLM repeated measure models showed the opioid group annual health expenditure was 2.65 times than the non-opioid treatment group for BCBSTX sample.

For the longitudinal setting, the descriptive analysis for the difference of annual health expenditure increase of new-opioid episode group was $5,599 for the MEPS data and $7,679 for the BCBSTX data. The GLMMs model showed MEPS had $5,468 increase for opioid treatment group than the non-opioid treatment group, and the BCBSTX assessed the increase of the health expenditure for new-opioid group was $6,625 higher than the non-new opioid group, after adjusted for all the covariates.

Table 19 Opioid Treatment Related Health Expenditure Comparisons in Cross-sectional and Longitudinal settings.

Data Source		MEPS	BCBSTX
Cross-sectional			
	Δ of annual health expenditure*	$23,413	$ 9,193
	OLS	N/A	$ 8,103
	GLM	N/A	2.65 times
Longitudinal			
	Δ of annual health expenditure increase	$5,599	$7,679
	GLMMs	$5,468	$ 6,625

*Cross-sectional MEPS part did the comparison after PS matching and no regression, and the BCBSTX did multivariate regressions and not PS matching.

Both data sets showed long-term opioid treatment had higher health expenditure or larger increase. The approach to calculate the MEPS annual health expenditure included all types of health expenditure, and the BCBSTX only included claims payment. Since the BCBSTX total expenditure was not as comprehensive as the MEPS's, the BCBSTX estimations was lower than the MEPS. But all the difference or changes were in the same direction and the GLM times estimation were very similar.

In the longitudinal analysis for both datasets, the study also explored the difference of annual health expenditure change between new-CNCP diagnosis group and non-new CNCP diagnosis group. The difference was $1,237 increase for MEPS and was $7,051 more increase for BCBSTX in the descriptive analysis. After adjusted for demographic, SES, comorbidity and comorbidity and health status, the MEPS GLMMs model showed the new-CNCP group annual health expenditure was $2,590 increase than the non-new CNCP group. The BCBSTX CLMMS model assessed the increase of the health expenditure for new-CNCP group was $2,567 higher than the non-new CNCP group, after adjusted for all the covariates.

For the emergency department visits, the MEPS data compared annual ER expenditure difference and change. The MEPS cross-sectional results showed the opioid group annual ER expenditure was $911 higher than then non-opioid group. The MEPS longitudinal results showed the new-opioid group was $27 higher increase of annual ER expenditure than the non-new opioid group, and the new CNCP group was $15 higher than the non-new CNCP group.

The BCBSTX data compared the difference and change of the annual ER visits count. There were 24% patients had ED visit yearly for the long-term opioid CNCP group, and 15% for the non-opioid group. The opioid group is 9% higher than the non-opioid group (Pr>t=0.00). For the patients with ED, the average yearly total ED visit count for long-term opioid CNCP patients were 3 and for non-opioid treatment were 2 (Pr>t=0.00). The study also compared the count change (increase or decrease) of yearly ED visits before and after the new CNCP diagnosis. There was 0.28 increase for patients with new CNCP diagnosis and 0.07 decrease for patients who did not have new CNCP diagnosis (Pr>t=0.00). In addition, the study also checked the count difference of yearly ED visits before and after the initiation of new opioid episode. There was 0.28 increase for patients started new long-term opioid treatment and 0.02 decrease for patients did not have long-term opioid treatment (Pr>t=0.00).

5.2 Strengths and Limitations

One of the strengths of this study is the cross-validation of findings from different data sources. The MEPS data contains national sample survey of families and their medical providers across the United States, which is a very complete data source for the cost and utilization of the healthcare services. The MEPS has rich data components to capture the demographic factors, SES characterizes, chronic disease conditions and health behaviors for the risk adjustment. The MEPS also includes both medical and pharmacy claims data to reflect the detailed services breakdowns. The MEPS sample includes people with either private or public insurance. Also, the MEPS

panel data structure enables the longitudinal analysis cross different years to generate robust estimation of the causal relationship. On the other hand, the BCBSTX claims dataset is a regional private insurer's administrative data, which offsets the reporting bias of self-reported MEPS data. The BCBSTX claims dataset covers 1/3 of the commercial insurance in Texas, which contains all medical and pharmacy claims for both professional and facility claims for BCBSTX members living in Texas under 65 years old. By using five years BCBSTX record, this study is able to track the change of health conditions and medical services utilization over time.

Another strength of this study is adopting both cross-sectional and longitudinal models to test the hypothesis of correlation ship between increase of health expenditure and long-term opioid treatment for CNCP patients. The cross-sectional model compared total annual health expenditures for long-term opioid treatment CNCP patients and non-long-term opioid treatment CNCP patients with same characteristics after PS-match and adjusted for all the potential cofounders. The longitudinal model checked the difference of total annual health expenditures for the same individuals before and after the new diagnosis of CNCP condition or initiation of new opioid treatment for CNCP patients, which excluded the difference for many characteristics at individual level since the comparisons were for the same patients pre- and post- initiation of new opioid treatment episode or diagnosis of new CNCP conditions. The longitudinal outcomes reveled the real relationship between opioid treatment and the change of health expenditures.

Additional strength of the study is that the outcome variable of this study incorporated both health expenditure in dollar value and the counts of adverse event. The

money value can be used directly to estimate the national level healthcare opportunity cost for long-term opioid treatment. The comparison of adverse event (ER visits) count for treatment and control groups can provide more insight about where those higher cost comes from for the opioid group, and the scale of the difference for various health utilization buckets. That information is useful for improvement of opioid treatment or CNCP management by reducing the high cost adverse events.

In Oct 2018, the Senate approved Dubbed the Support for Patients and Communities Act to address the opioid epidemic, following the House's approval. The legislation is considered as a big breakthrough that will enhance access to addiction treatment and boost many interventions to impede the current opioid epidemic. The interventions cover law enforcement efforts against opioid abuse and combating the illegal opioid prescription. Even though, the legislation aims to make addiction treatment more accessible, to reduce the illicit synthetic opioid, and to encourage non-opioid pain treatment, the bill does not expand payment for addiction treatment and would not provide significant increase in spending for the opioid crisis. Considering the limited funding environment, the outcomes of this study provided decision makers an estimation about the direct cost and the potential savings for long-term opioid treatments. They can use that information to optimize the spending in different measures to combat the opioid crisis.

Last, this study also appraised new incidences of CNCP condition and of the long-term opioid treatment, which could be populated to assess the national or regional health expenditure associated with the conditions and the treatment.

Several limitations should be noted. First, due to the constraint of the data, it was difficult to distinguish the opioid abuse and the regular opioid treatment. Thus, the results were impossible to distinguish the impact of normal opioid treatment and the opioid addiction/ abuse. As well, the comparison of health expenditures between opioid treatment and non-opioid treatment groups was among CNCP patients, which did not cover the opioid abuse patients without the CNCP conditions. Since this work mainly focused on the impact of regular long-term opioid treatment on CNCP patients not the impact of opioid abuse, this should not have biased the findings.

Second, I did not adjust for all the potential confounders for the causal relationship between the opioid/CNCP and total medical expenditure, because the BCBSTX data set files do not include enough detail to implement the exact same risk adjustment as the MEPS data. Using risk adjustment would not affect underlying health expenditure, but it would lead to the more variability in the expenditure comparison.

Third, this study only used the private insurance claim date to validate the self-reported health utilization date. There might be some selection bias or geographic difference for the private claim sample and the MEPS sample. Also, the Medicare and Medicaid claims data were not included in the analysis, which might make the comparison more complete. In the future, it will enhance our results if we could add public insurance claim data to the analysis.

5.3 Conclusion

Chronic pain is one of the most prevalent reasons for doctor visits. In the national opioid crisis, it would be informative to not only understand the effectiveness of the opioid treatment, but also the potential cost of treatment. It is critical to investigate the health expenditure difference for opioid treatment when there has been lack of evidence to prove the long-term opioid treatments for CNCP as the best practice. By using 2011 Medical Expenditure Panel Survey data and 2008-2012 Texas Blue Cross Blue Shield claim data. This study showed higher summed medical expenditures for CNCP patients. Moreover, this work proved long-term non-cancer pain could lead to economic, societal and health impacts. The opioid treatment for chronic non-cancer pain is related to higher medical spending and more emergency department visits. In the national fight against the opioid epidemic, it is critical to know the economic impact of long-term opioid treatment. This study not only proved the high medical spending of CNCP conditions, but it also underscores the increase of cost to the health care system for the long-term opioid treatment. And highlight the need for cost-effective pain treatments.

Although there are some limitations of this analysis, the outcomes gave policy makers, payers, physicians, and CNCP patients insights about potential expenditure difference with and without the opioid treatment. Different from other studies focused on certain types of chronic pain, this estimation was for all types of CNCP by using both ICD diagnosis code and SF-12 Questionnaire. Policy makers could use this estimation to assess the social cost for the opioid treatment and accordingly make change of the opioid management. Payers could use this outcome to adjust the reimbursement. Physicians

could share this information with patients to help patient deciding on an appropriate CNCP management strategy.

Although there are some limitations of this analysis, the outcomes give policymakers, payers, physicians, and CNCP patients insights about potential expenditure difference with and without the opioid treatment. Different from other one data sources study, this study analyzed both private insurance claims data and national survey data, which enhanced the validity and reliability of the outcomes.

As one of the health economists, our main responsibility is to optimize the health care resources allocation in an effectively and efficiently way, under the limitation of funding, staff and facilities. The finding of this study showed quantified evidence of the impact for long-term opioid treatment. It gave solid proof of higher health expenditure and utilizations for opioid for CNCP patients. It could be used for comparison of different CNCP treatment approaches, by contributing cost information for incremental cost-effusiveness ratio.

Policymakers could use this estimation to assess the social cost for the opioid treatment and accordingly make change of the opioid management. Payers could use this outcome to adjust the reimbursement. Physicians could share this information with patients to help patient deciding on an appropriate CNCP management strategy. My results underscore the high cost of opioid treatment to the health care system and highlight the need for cost-effective CNCP treatments.

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