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The Prescribing Patterns of Gabapentin and Pregabalin in a Medicaid Population Amid the Opioid Epidemic

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THE PRESCRIBING PATTERNS OF GABAPENTIN AND PREGABALIN IN A MEDICAID POPULATION AMID THE OPIOID EPIDEMIC

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ABSTRACT

OBJECTIVE: Drug overdoses continue to be the leading cause of accidental death in the United States resulting in a nationwide crisis. Opioids, many of them prescription, are now the primary cause of drug overdose related deaths. Gabapentinoids are being promoted by the Centers for Disease Control and Prevention as a safer alternative to opioids and have steadily been rising in prescribing rates. However, growing concern is mounting on the potential for gabapentinoid misuse. The goal of this dissertation was to deepen the knowledge and understanding of how gabapentinoids are currently being prescribed, with an emphasis on their co-prescribing with an opioid drug and potential negative outcomes.

METHODS: This study identified trends in the prescribing of gabapentinoids, specifically gabapentin and pregabalin, through a cross-sectional retrospective cohort analysis using South Carolina Medicaid data from 2009-2016. The analysis investigated demographic variances, prescribing rates, and prescription characteristics. Bivariate and multivariate logistic linear regression was utilized to identify potential predictors of the concomitant prescribing of a gabapentinoid and an opioid and subsequent overdose events.

RESULTS: Total gabapentinoids dispensed to South Carolina Medicaid beneficiaries increased from 23,204 in 2009 to 86,649 in 2016. Nearly 70% of

patients were also administered an opioid concomitantly. Patients prescribed pregabalin (OR=1.367; CI:1.175–1.592), high gabapentinoid dosages (OR=3.088; CI:2.398–3.975), and long term gabapentin (OR=3.336; CI:2.949-3.774) or pregabalin therapy (OR=6.555; CI: 3.962-10.875) increased likelihood of opioid coprescribing. Concomitant prescribing was associated with an increased likelihood of opioid overdose (OR=1.223 CI: 1.014-1.476).

CONCLUSIONS: Gabapentinoid prescribing in South Carolina's Medicaid has significantly increased in recent years. Concomitant prescribing of an opioid and a gabapentinoid is extremely common and more likely when prescribed at higher dosages and for extended periods of time. Patients coprescribed an opioid and gabapentinoid appear to be at a higher risk of opioid overdose. Increasing physician awareness regarding the potential adverse effects of opioid and gabapentinoid concomitant administration, coupled with additional monitoring of gabapentinoids, is recommended to ensure safe prescribing of these medications.

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LIST OF ABBREVIATIONS

ADF ..... Abuse Deterrent Formulation

AHFS ..... American Hospital Formulary Service

CDC ..... Centers for Disease Control and Prevention

CMS ..... Centers for Medicare and Medicaid Services

CPT ..... Current Procedural Terminology

CNCP ..... Chronic Non-cancer Pain

CNS ..... Central Nervous System

CS ..... Controlled Substance

DEA ..... Drug Enforcement Administration

DHEC ..... Department of Health and Environmental Control

DPN ..... Diabetic Peripheral Pain

DSM-V/5 ..... Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

GBP ..... Gabapentin

GDD ..... Gabapentinoid Daily Dosage

HCPCS ..... Healthcare Common Procedure Coding System

HIC ..... Health Insurance Claim

ICD-9 ..... International Classification of Diseases, Ninth Revision

ICD-10 ..... International Classification of Diseases, Tenth Revision

NIH ..... National Institute of Health

NPI ..... National Provider Identifier

MEDD ..... Morphine Equivalent Daily Dosage

PDMP ..... Prescription Drug Monitoring Program

PRG ..... Pregabalin

SAMHSA ..... Substance Abuse and Mental Health Services Administration

SC. ..... South Carolina

SCDHHS..... South Carolina Department of Health and Human Services

SCRIPTS ... South Carolina Report and Identification Prescription Tracking System

SSI..... Supplemental Security Income

US ..... United States of America

CHAPTER 1

INTRODUCTION

1.1 Background

For over a decade, drug overdoses have been the leading cause of accidental death; more than motor vehicle accidents, fire arms, or falling (CDC, 2016). Opioids, many of them prescription, are now the primary cause of drug over-dose related deaths, resulting in a nationwide crisis (Grattan, 2012). The prescription opioid epidemic has continued to increase in severity, with over 16,000 people dying annually from prescription pain relievers (CDC, 2016; NIH, 2017). This increase in mortality rates has been ascribed in large part to the 400% increase in opioid pain medication prescribing rates (CDC MMWR, 2011). Efforts to reduce mortality rates have included: increased access to treatment for those suffering from dependence and abuse, increased access to life saving over-dose reversal medication, and limits on opioids dispensing (Buck, 2011; Chin Hwa Y. Dahlem PhD, 2015; Jeffrey A. Gray, 2012; Thomas F. Babor PhD, 2007). However, the U.S. still consumes over 99% of the worlds hydrocodone and 80% of its oxycodone, while constituting less than 5% of the world's population (Board, 2016).

South Carolina (SC) is highly impacted by the prescription opioid epidemic, ranking 9th in the nation for opioid prescribing rates in 2016, accounting for nearly

5 million opioid prescriptions filled (CDC, 2017; DHEC, 2017). The Medicaid population is especially at-risk of receiving a prescription for an opioid drug. A 2016 report from Express Scripts-- the largest pharmacy benefit management organization in the U.S.-- found that one in four Medicaid beneficiaries received an opioid prescription in the previous year, with nearly a third co-prescribed a benzodiazepine or muscle relaxer (ExpressScripts, 2016).

As efforts to decrease opioid utilization continue, it will be of critical importance to understand changes to prescribing patterns, especially as opioid-alternative medications increase in popularity. These alternative medications warrant investigation as they themselves may pose a risk for adverse events. Understanding the changing landscape in these prescribing patterns and the potential for negative outcomes will aid health care professionals in decisions surrounding their dispensing and ensure efforts aimed at reducing opioid prescribing maximize benefits and minimize harms to the impacted populations.

1.2 Gabapentinoids

Gabapentin and pregabalin--sold by Pfizer under the brand names Neurontin and Lyrica respectively--are medications approved by the Food and Drug Administration (FDA) to treat epilepsy and certain types of neuropathic pain (Mack, 2003; Toth, 2014). Often referred to as gabapentinoids, these medications are also routinely prescribed "off-label" for a variety of other conditions, including depression, migraines, and bipolar disorder (Christine Fukada, 2012; Radley DC, 2008; Sabioni P, 2015). Gabapentinoids are being promoted by the Centers for

Disease Control and Prevention (CDC) as a "safer" alternative to opioids (CDC, 2016a; Dowell D, 2016). In addition, The American Pain Society recently recommended that gabapentin be considered for post-operative pain relief (Roger Chou, 2016). These medications have been steadily rising in prescribing rates. Gabapentin prescriptions dispensed at U.S. pharmacies increased over 50% in only 4 years and is now the 10th most prescribed drug in the U.S. (Christopher W. Goodman, 2017; Institure, 2017). Additionally, pregabalin doubled in total sales during the same time period (Christopher W. Goodman, 2017; Institure, 2017). Figure 1.1 depicts the recent increase in prescribing and spending on these medications.

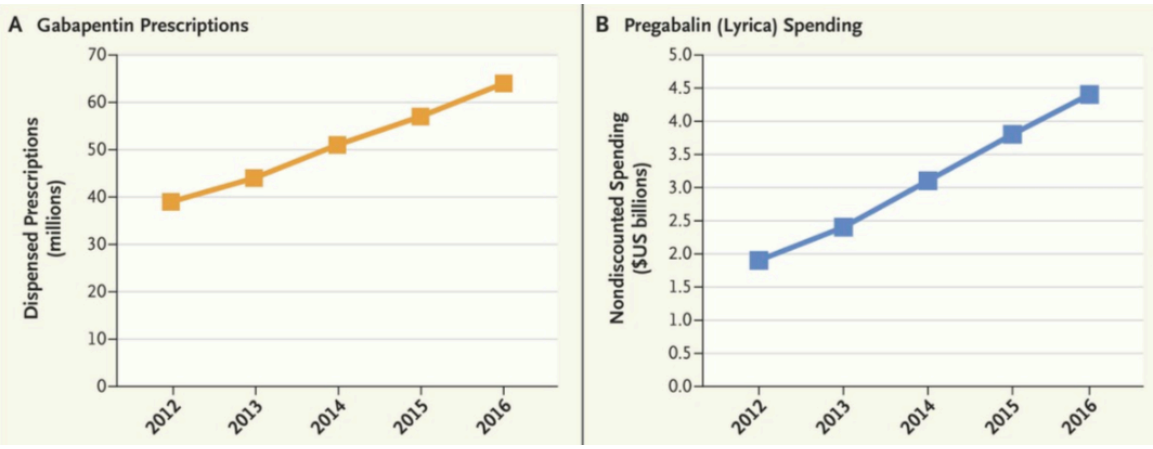

Figure 1.1 Prescriptions filled at US pharmacies for gabapentin and US spending on pregabalin, 2012-2016.(Christopher W. Goodman, 2017)

Gabapentinoids have historically been described as having little to no abuse potential. Gabapentin is currently unscheduled and pregabalin is a Schedule V medication, indicating the lowest abuse potential of scheduled drugs by the Drug Enforcement Administration (DEA) (Bonnet U, 1999; Jill E. Lavigne, 2012).

Recently, questions have been raised on whether gabapentinoids are truly as abuse-resistant as previously thought. Reports have revealed user accounts of gabapentinoids eliciting a similar high obtained from other central nervous system (CNS) acting drugs (Baird CR, 2014; Kirk E. Evoy, 2017). In addition, recent studies have suggested that gabapentinoids may potentiate the high obtained from CNS drugs such as morphine, enhancing effects (Eckhardt K1, 2000; Roy R. Reeves, 2014). When abused, gabapentinoids are typically self-administered at doses much higher than therapeutically prescribed in efforts to produce the associated euphoric effects (Bastiaens L, 2016). A 2015 study of non-medical opioid users in Appalachian Kentucky found 15% of respondents admitted to using gabapentin to get high (Rachel V. Smith, 2015). In July 2017, Kentucky became the first state to classify gabapentin as a Schedule V controlled substance (Commission, 2017).

An additional recent study utilizing toxicological data found one in five patients were taking gabapentin illicitly (K. Quigley, 2016). The high rate of misuse of this medication is surprising and a wakeup call for prescribers. Providers dont usually screen for gabapentin abuse when ensuring patients are taking medications, such as opioids, as prescribed. These findings reveal that there is a growing risk of abuse and a need for more robust testing. Researchers found that of those patients taking gabapentin illicitly, over half (56%) were taking it with an opioid and more than a quarter (27%) with an opioid and muscle relaxant or anxiety medication. The data came primarily from pain clinics in Indiana, Arizona,

and Massachusetts. While the investigation into gabapentin misuse and abuse is limited, even less is known on the illicit use of pregabalin, which is estimated to be 5 times more potent than gabapentin, making the possibility for abuse potentially even higher (Keyhanfar, 2013).

1.3 Research Objectives

These previous findings have shown that a significant number of patients are taking gabapentinoids without physician consent and/or combining them with an opioid drug. These abuse trends parallel the rise in reported diversion rates and post-mortem incidence rates of gabapentinoids (Buttram ME, 2017; Kirk E. Evoy, 2017). It will be of increased importance to understand the implications of the rapid rise in gabapentinoid prescribing and its potential negative outcomes. With the 9th highest opioid prescribing rate, South Carolina has a high potential for co-prescribing of gabapentinoids (DHEC, 2017). In addition, South Carolina has a diverse demographic landscape which allows for the examination of patterns within various socioeconomic levels. And as noted previously, the Medicaid population is particularly vulnerable, with 1 in 4 beneficiaries prescribed an opioid (ExpressScripts, 2016). Therefore, South Carolina's Medicaid population will allow insight into prescribing patterns in various populations and ultimately potential health impacts.

The goal of this dissertation is to deepen the knowledge and understanding of how gabapentinoids are currently being prescribed with an emphasis on co-prescribing with an opioid drug and potential negative outcomes. This study will

investigate the following aims utilizing Medicaid data from the South Carolina Revenue and Fiscal Affairs Office, for years 2009-2016. Specifically, using the South Carolina Medicaid population, this study seeks:

- Aim 1: To determine the prescribing patterns of gabapentinoids (gabapentin and pregabalin).
- Aim 2: To determine rates and trends of the co-prescribing of a gabapentinoid with an opioid.
- Aim 3: To identify factors associated with an increased likelihood of gabapentinoid and opioid co-prescribing.
- Aim 4: To determine if there is an association between the co-prescribing of a gabapentinoid and opioid and emergency department visits due to overdose.

This study will provide valuable insight to providers prescribing gabapentinoids in South Carolina and the Medicaid population at large, and help to fill the knowledge gap of these relatively unstudied medications. Identifying opioid alternatives to effective pain management treatment is of crucial importance to fight the opioid epidemic. However, health care professionals must also understand the potential risks associated with the prescribing of gabapentinoids, especially in the most vulnerable populations.

CHAPTER 2

BACKGROUND AND LITERATURE REVIEW

Chapter two is divided into three major subsections. Background on the opioid epidemic in the United States (US) is presented in subsection one. This includes a brief history of the rise in opioid utilization and an overview of the epidemics current status. The second subsection outlines risk factors associated with opioid abuse and overdose. The final subsection comprises an overview of gabapentinoids and their utilization as an alternative to opioids in addition to a comprehensive literature review. The literature review will outline the growing body of evidence suggesting the abuse potential of gabapentinoids.

2.1 The Opioid Epidemic in the U.S.--Background and Current Status

This subsection first describes the history of opioids, both natural and synthetic, and their rise in utilization beginning in the twentieth century. Also presented is an overview of federal drug policy and interventions aimed at curbing illicit usage. The section goes on to describe the environment that led to the belief in the late 1990s that certain opioids had little to no abuse potential which in part resulted in skyrocketing prescribing rates. Finally, the subsection concludes with an overview of the current status of the opioid epidemic.

2.1.1 Opium: The Original Opioid

Opioids have been utilized for both their medical and euphoric effects for millennia. The poppy plant, often recognized for their bright red flower, contains naturally occurring opioids. Historians generally agree that by the end of the third millennium B.C., poppies were being cultivated for the isolation of opium (Brownstein, 1993). The opium isolation process would become more refined and subsequently be utilized as an additive in tonics, wine, and early medications (Cumston, 1988; Hodgson, 2001; Brooke, 2017). By the early 1800s chemical advances allowed for the identification and isolation of the active ingredient in opium, fittingly named morphine -- after Morpheus, the Greek god of sleep (Brooke, 2017). However, although the potency and efficacy of morphine had drastically increased due to its isolation, it would not become widely utilized until the invention of the hypodermic needle in the mid nineteenth century (Brownstain, 1993). Following this rise in popularity, pharmaceutical manufacturers began to explore opiate derivatives and in 1898 Bayer released a new medication that would soon overtake even morphine in popularity—heroin (Musto, 1991).

2.1.2 Federal Intervention

The soaring popularity of morphine and heroin in the early 20th century would lead to Americas first opioid crisis. The highly addictive nature of these medications was soon discovered, leading to dependence and abuse among users (Courtweight, 1982). Several federal measures would be enacted to combat the rise in morphine and heroin abuse and misuse. In 1924, the Heroin Act would

prohibit the manufacturing and possession of heroin (Berridge, 1999). Later, in 1938, the FDA would be granted significantly greater regulatory authority to ensure the safety of all medications and advertising claims (FDA.gov). Even with this newly appointed authority, the FDA continued to approve opioid derivatives throughout the mid-1900s, notably hydrocodone in 1943 and oxycodone in 1950 (FDA.gov). It would be decades before the dependence and addiction potential of opioids would be fully understood.

The 1970s brought further federal regulation. The Comprehensive Drug Abuse Prevention and Control Act of 1970 expanded the scope of drug policy--regulating the production, possession, and use of defined controlled substances. Title II of this Law, The Controlled Substance Act, created five schedules (C-I through C-V) that classified both illicit and pharmaceutical substances based on their potential for abuse, with Schedule I drugs deemed the most dangerous. Access is more tightly controlled for prescriptions that are designated a controlled substance. Based on schedule, limitations may include length of supply limits, refill restrictions, and requiring the patient to present a hard copy of the prescription. Table 2.1 outlines the differences in scheduling and common substances per classification. The DEA and FDA are jointly responsible for addition, removal, or change in schedule of any drug.

Table 2.1 List of DEA Scheduling Classifications.

Schedule	Definition	Example Drug
C-I	No currently accepted medical use and a high potential for abuse. No approved medical use.	• Heroin • MDMA (Ecstasy) • LSD
C-II	High potential for abuse, with use potentially leading to severe psychological or physical dependence.	• Amphetamine • Hydrocodone combination products • Methadone • Oxycodone
C-III	A moderate to low potential for physical and psychological dependence.	• Anabolic steroids • Ketamine • Testosterone
C-IV	A low potential for abuse and low risk of dependence.	• Alprazolam • Diazepam • Carisoprodol • Tramadol
C-V	Lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics.	• Lower strength codeine products • **Pregabalin**

**Note Gabapentin is currently unscheduled by the DEA.

2.1.3 Conflicting Messaging on Opioid Abuse

Although increasing federal regulation began to highlight the hazardous nature of opioids, there was still debate among the medical community on their addictive properties. In 1980, a small letter in the correspondence section of The New England Journal of Medicine would lead to a gross misrepresentation of the potential risks of opioid addiction. A physician and his graduate assistant at Boston University, Dr. Hershel Jick and Jane Porter, conducted a retrospective longitudinal study of hospital patients who were prescribed a narcotic. They concluded "despite widespread use of narcotic drugs in hospitals, the development of addiction is rare

in medical patients with no history of addiction." (Porter and Jick 1980). This five-sentence summary in the Journal's letter to the editor section would go on to be cited over 600 times. It would often be used for evidence on the rarity of addiction in all patients prescribed opioids, failing to indicate the specific population studied in the investigation (Leung 2017). Citations of the Porter and Jick letter spiked significantly in 1996, the same year the pharmaceutical company Purdue Pharma launched OxyContin into market (Leung 2017).

OxyContin would forever change the opioid landscape. The marketing campaign that Purdue Pharma rolled out for OxyContin was unprecedented. Purdue doubled its sales force in only 4 years and utilized complex marketing data to target the highest opioid-prescribing physicians (Van Zee, 2009). Once identified, these physicians received free promotional merchandise and all-expense paid symposium trips. Promotional print-outs and videos were aggressively distributed. The most troubling marketing material promoted OxyContin as having very limited abuse potential--as low as "less than one percent" (Van Zee, 2009).

2.1.4 Increased Attention to Pain Management

During this same time-period the "Fifth Vital Sign" campaign was increasing in popularity. In 1995, during a presidential address to the American Pain Society, Dr. James Campbell introduced the idea of assessing pain as a vital sign (Morone 2013). The American Pain Society would begin the "Fifth Vital Sign" campaign to bring attention to undertreated pain. In 2001, The Joint Commission released its Pain Management Standards, calling for healthcare providers to assess pain in each

patient (JCAHO, 2001). Recommendations included assessing pain using a ten-point scale to ensure adequate care was being delivered.

Increased awareness of proper pain management was making national headlines. A 2001 article published by Time Magazine entitled "Less Pain, More Gain" furthered the idea that pain was undertreated and the risk of addiction from opioid medications low (TIME, 2001). The article cited the "landmark study" by Porter and Jick and used it as evidence that there is an "exaggerated fear that patients would become addicted" to opioid narcotics and that the fear is "basically unwarranted".

Increased attention on pain management, unprecedented opioid marketing campaigns, and an understated risk of abuse potential led to an environment where opioid prescriptions written in the U.S. skyrocketed. From 1999 to 2010 opioids dispended at U.S. pharmacies nearly quadrupled (CDC MMWR, 2011). During this time period, drug overdose deaths would become the leading cause of accidental death, with more than 140 fatal overdose deaths per day (CDC 2016). By 2015, prescription drugs would surpass mortality rates of illicit drugs and account for over 50% of all overdose fatalities (CDC, 2015).

In an effort to curb misuse, abuse-deterrent formulations (ADFs) of opioids began to enter the market. A notable ADF was the reformulation of OxyContin, which made the medication more difficult to dissolve or crush for intravenous use. After the reformulation of OxyContin, abuse rates did decrease, however drug

overdose fatalities overall continued to rise as addicted users transitioned to the cheaper, and often more easily attained, heroin (Cicero, 2015).

2.1.5 Current State of the Opioid Epidemic

The abuse and misuse of opioids continued to rise into the twenty-first century and is now a leading health concern in the U.S. More than one third of the adult population receives a prescription pain medication annually (SAMHSA, 2017). Fueled in part by the increasing availability, drug overdoses have been the leading cause of accidental death for more than a decade--more than motor vehicle accidents, fire arms, or falling. Overdose fatalities remain at an all-time high with over 40,000 fatalities involving an opioid (both prescription and illicit) occurring in 2016 (CDC, 2017). As overdose fatality rates rose, so too did the rates of non-fatal abuse and misuse of these medications. From 1997 to 2007, admission rates for prescription medication substance abuse increased nearly 500% (SAMHSA, 2009). There are now an estimated 11 million people misusing prescription pain relievers annually (SAMHSA, 2017).

The economic burden of the opioid epidemic has also reached staggering proportions. Individuals abusing opioids are known to have substantially higher health care costs---8 times more than individuals who do not have a substance use disorder (Strassels, 2009). The U.S. Council of Economic Advisers recently released a report stating that previous assessments of the opioid epidemics total economic burden had been underestimated. They estimate the economic burden to be over 500 billion dollars when all aspects of the epidemic are taken into

consideration including costs associated with healthcare, criminal justice, lost productivity, and VSL (value of a statistical life).

Several federal strategies have been aimed at combating the opioid epidemic. A multi-faceted approach has included: (1) increasing access to both medication-assisted treatment (MAT) and overdose-reversing drugs, (2) strengthening research and data reporting, (3) reducing opioid overprescribing, and (4) education initiatives for both patient and prescriber (NIH, 2017). Many of these initiates focus on reducing the number of filled opioid prescriptions. New guidelines for prescribing opioids for chronic pain were released by the CDC in 2016. Included in these guidelines were recommendations on appropriately prescribing opioids and non-opioid pharmacological treatment alternatives. Provider prescribing behavior will continue to be a critical component to reducing the overdose fatalities.

2.2 Risk Factors of Opioid Abusers and Fatal Overdoses

This subsection first outlines the clinical definition and distinctions of substance use disorders. A range of aberrant substance use behaviors which have unique characteristics and considerations are then presented. The section goes on to describe previous studies which have identified potential individual risk factors and populations particularly at risk for substance abuse including socio-economic demographics, physician variances, and geographical differences, among others.

2.2.1 Defining Substance Use Disorders

The "Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition", often referred to as DSM-5 (or DSM-V) remains the primary resource for classifying mental disorders including substance use disorders (DSM-V, 2013). This resource gives criteria for the diagnosis of substance abuse and dependence disorders. The DSM-5 proposes that the brains reward system is a common feature among all drug abuse. The mechanism of action may differ from drug to drug, however, the resulting pleasure or euphoria from the drug reward pathway remains consistent. The 11 criteria of substance use disorders defined by DSM-5 is outlined in Table 2.2.

The severity of the substance use disorder is indicated by the number of positive criteria (2-3 mild, 4-5 moderate, 6+ severe). These 11 criteria are utilized in the identification and diagnosis of substance abuse disorders.

Table 2.2 DSMs 11 criteria of substance use disorders.

1. Taking the substance in larger amounts or for longer than you meant to.
2. Wanting to cut down or stop using the substance but not managing to.
3. Spending a lot of time getting, using, or recovering from use of the substance.
4. Cravings and urges to use the substance.
5. Not managing to do what you should at work, home or school, because of substance use.
6. Continuing to use, even when it causes problems in relationships.
7. Giving up important social, occupational or recreational activities because of substance use.

8. Using substances again and again, even when it puts you in danger.
9. Continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by the substance.
10. Needing more of the substance to get the effect you want (tolerance).
11. Development of withdrawal symptoms, which can be relieved by taking more of the substance.

2.2.2 Defining Aberrant Substance Use Behaviors

Aberrant substance use behaviors are described in the literature by a variety of different terms. This differing language can lead to confusion on the severity and particularities of the substance use behavior. The Substance Abuse and Mental Health Services Administration (SAMHSA) builds upon the criteria set by the DSM-5 and defines common terms used to describe non-medical substance use. This study will utilize these proposed definitions when describing aberrant substance use behaviors.

Table 2.3 Definitions of Aberrant Substance Use Behaviors

Aberrant Substance Use Behavior	Definition
Nonmedical use	Use of prescription drugs that were not prescribed by a medical professional (i.e., obtained illicitly) or use for the experience or feeling a drug causes.
Misuse	Incorrect use of a medication by patients, who may use a drug for a purpose other than that for which it was prescribed, take too little or too much of a drug, take it too often, or take it for too long (misuse does not apply to off-label prescribing).

Abuse	A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by one or more behaviorally based criteria.
Physiological dependence	Increasing tolerance for a drug, withdrawal signs and symptoms when a drug is discontinued, or the continued use of a substance to avoid withdrawal. A set of psychological symptoms that demonstrate overall loss of control or obsessive-compulsive drug-seeking and continued use of a substance in spite of clearly adverse consequences.
Pseudoaddiction	Drug-seeking and other behavior that is consistent with addiction but actually results from inadequate pain relief. Once the pain is adequately treated, the person no longer abuses the medication.

Source: SAMHSA Substance Abuse Treatment Advisory Volume 5.2, 2006

2.2.3 Risk Factors

The characteristics of individuals using opioids non-medically and the demographic breakdown of fatal overdoses have been investigated in detail. Below is a summary of risk factors associated with opioid abuse, misuse, and overdose.

i. Sex/Gender: Overdose fatality data consistently shows that men are at increased likelihood of opioid misuse and overdose death than women (KFF, 2017; Kaplovitch, 2015; Cochran, 2014; White, 2009). In 2016, 67.5% of all opioid overdose deaths were male (KFF, 2017). However, risk of non-fatal opioid abuse and misuse is less clear. Studies have found that woman may be more susceptible to addiction. A study of 892 individuals in MAT therapy for opioid dependence found women were significantly more likely to report

cravings. (Back, 2011). In a larger 33 state-wide study of 5,663 patients in a methadone maintenance treatment program, women were more likely to report prescription opioid abuse than men (Rosenblum, 2007). A multi-year study of nearly 30,000 treatment center assessments found similar results, with women more likely to report opioid use and misuse in the past 30 days. (Green, 2009).

ii. Race and Ethnicity: White non-Hispanic individuals accounted for nearly 80% of all opioid overdose fatalities in 2016 (KFF, 2017). This group was more likely to report misuse or abuse of opioids in both a primary care and medication assisted treatment setting (Liebshult, 2010; Fleming, 2007; Boscarino, 2010). This may be in part that white patients are more likely than all other racial groups to receive an opioid medication in both an emergency department (ED) and primary care setting (Pletcher, 2008; Olsen, 2006).

iii. Age: Historically, a strong inverse relationship has been observed with opioid abuse and dependence (Edlund, 2010; White, 2009). However, the age disparity has been shrinking in recent years. Fatal overdoses in the 55+ population nearly doubled in the last decade, rising from 10% of total overdoses in 2005 to 19% in 2015 (KFF, 2017). The only other age category to significantly increase during this time was the age group 25-34 years, rising from 20 to 26%, and

the age group now accounts for the highest proportion all fatal opioid overdose fatalities.

iv. Opioid Dosage and Length of Supply: The opioid dosage and length of supply have been shown to have an association with long term abuse of opioids and overdose death. Morphine Equivalent Daily Dosage (MEDD) (a normalized measure of opioid potency) consistently shows a strong association with both overdose deaths and the potential for abuse and misuse—with an MEDD of >120 having the highest impact (Liang, 2009; Bohnert, 2011; Buamblatt, 2014; Edlund 2014; White 2009). Additionally, an increase in the days supplied has also been associated with an increase in likelihood of opioid misuse (Shah, 2009; Edlund, 2014; Cochran, 2014).

v. Diagnoses: Diagnoses are often included in analyses that aims to determine predictive characteristics for opioid abuse and overdose. It is well documented that individuals with a history of substance abuse (illicit or prescription) have a higher likelihood of opioid abuse or misuse. (Edlund, 2010; Dunn, 2010; Manchikanti, 2007; White 2009). A previous diagnosis of a mental health disorder is also significantly associated with an increased likelihood of an opioid misuse disorder (Dufour, 2014; Cochran, 2014; Barth, 2008; White, 2009).

2.2.4 Physician Influences

Physician factors can influence prescribing and subsequent utilization of opioids. There is wide variation in prescribing rates of opioids among physicians, both within and between specialties (Barnett, 2017; Ringwalt, 2014; Dhalla, 2011). Variation has also been shown within the same specialty within a single hospital location (Barnett, 2017). Furthermore, opioid prescribing is highly variable even when physicians are met with identical case scenarios. (Tamayo, 2004). The physicians geographical region also plays a role in prescribing rates, with individuals in Appalachia and southern and western states more likely to be prescribed an opioid (Turk, 1994; Olsen, 2006, McDonald, 2012; Curtis. 2006). An increase in patient reported pain scores are associated with higher prescribing rates (Turk, 2002; Barnett, 2017) perhaps because physicians reported prescribing more opioids to increase patient satisfaction scores (Sinnenberg, 2017). Understanding physician prescribing patterns and practices is of critical importance since most opioids that are used nonmedically start with a legitimate prescription by one physician. Over 20% obtain them directly from one physician. Another 44% receive the medication free from a friend or family member who were themselves legitimately prescribed the medication (SAMHSA, 2014).

2.2.5 The Medicaid Population

Studies have shown that the Medicaid population is particularly vulnerable to opioid use disorders (Olsen, 2006). Medicaid recipients are significantly more likely to be prescribed an opioid when compared to those who are privately insured

(ACPM, 2011; NAMD, 2014; CDC, 2014). Medicaid beneficiaries are estimated to be up to 10 times more likely than private insurance beneficiaries to have an opioid misuse disorder (Ghate, 2010). In addition, annual medical costs for opioid abusers are estimated to be $6550 higher than non-abusers (McAdam-Marx, 2010; Ghate, 2010). A CDC study found that from 2004 to 2007, 45% of overdose fatalities in Washington State were Medicaid enrollees (CDC MMWR, 2009).

2.2.6 Opioids in South Carolina

South Carolina has the 9th highest opioid prescribing rate in the U.S. (DHEC, 2017). Misuse, dependence, and overdose rates have steadily risen over the past decade. In 2015, over 8,000 individuals were discharged from emergency departments for opioid related issues or overdose (DAODAS, 2017). Prescription overdose fatalities are up 18% from 2014, with opioids the major contributor in over 70% of all deaths (DHEC, 2018). Opioid related fatalities are now nearly double that of homicides in the state. In addition, there has been a substantial increase in the utilization of services from state-run substance abuse treatment facilities—up 135% in the past decade (DAODAS, 2017).

South Carolina has employed several initiatives to combat these rising trends. One of the first major initiatives was the implementation of the States Prescription Drug Monitoring Program (PDMP) in 2008 (SC DHEC). A PDMP is a state-wide electronic database that monitors controlled substance prescription. South Carolina's PDMP program is known as The South Carolina Report and Identification Prescription Tracking System (SCRIPTS). Pharmacies are required

to upload all controlled substances CII-CIV into SCRIPTS. By utilizing SCRIPTS, a prescribing provider can see all previous schedule II-IV controlled prescriptions filled by each patient. The program is aimed at reducing drug diversion and doctor-shopping behaviors while altering physicians' prescribing behavior. It also can alert the physician to any CS medication prescribed by another provider that may lead to adverse drug interactions.

2.3 Gabapentinoids

As the risks associated with opioids became well known and fatal overdose rates continued to soar, alternative medications for pain management care began to rise in prevalence and prescribing rates. Gabapentinoids, specifically gabapentin and pregabalin, became particularly popular. This subsection outlines the proposed mechanism of action of gabapentinoids and their commercial availability. A comprehensive review of literature focusing on the potential for abuse is then presented.

2.3.1 Pharmacokinetics of Gabapentinoids

Gabapentin and pregabalin are both analogues of gamma-amino butyric acid (GABA). The similarity in their chemical structure to GABA is shown in Figure 2.1. However, unlike GABA, they do not bind directly to GABA receptors (Manuef 2006). Rather, gabapentinoids bind to a subunit of voltage-gated calcium channels (alpha-2-delta) resulting in an inhibitory effect (Sills, 2006; Taylor, 2007). This subsequently reduces calcium influx and is believed to reduce neurotransmitter

release leading to their mechanism of action modulating abnormal neuron activity (Taylor, 2007; Evoy, 2017).

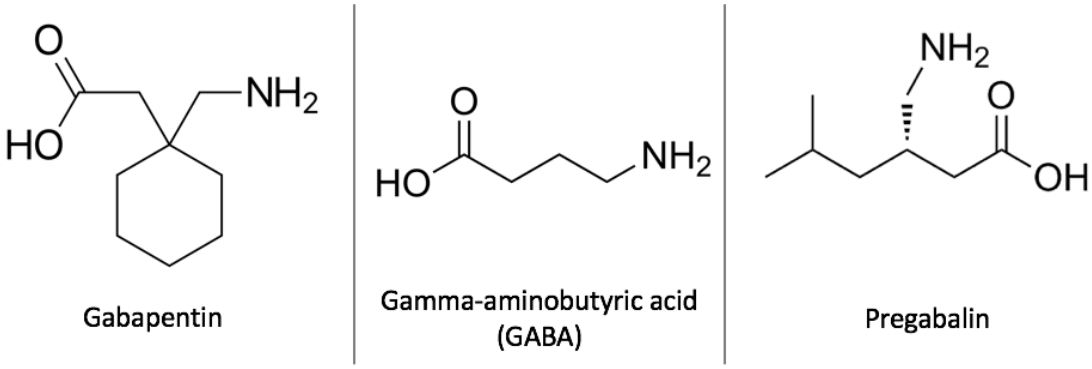

Figure 2.1. Chemical structure of gamma-aminobutyric acid, gabapentin, and pregabalin.

2.3.2 Overview of Gabapentin

Gabapentin, originally released in 1993 and sold under the brand name Neurontin by Pfizer, was initially approved by the FDA as an adjunct antiseizure medication (FDA). In 2004 it was additionally approved to treat neuropathic pain following shingles (FDA). Although gabapentin had limited FDA-approved indications, the medication has soared in popularity, predominantly for non-FDA approved uses. These off-label uses included: bipolar disorder, broad neuropathic pain, chronic pain, restless leg syndrome, migraines, drug and alcohol withdrawal, among others (Mack, 2003). A small investigation of patients in a managed Medicaid population showed 95% received gabapentin for an off-label diagnosis, most often chronic pain and mental health disorders (Hamer, 2002). The efficacy of gabapentin for off-label use is debated by healthcare professional, but in many

cases there is insufficient clinical evidence to support use for non-FDA approved indications (Mack, 2003; Hamer, 2002).

The high off-label prescribing patterns may stem in some part to an illegal marketing campaign by Warner and Lambert (a subsidiary of Pfizer) in 2004 in which they were eventually ordered to pay a fine of $430 million in USD. However, neither this discovery, nor the lack of evidence of efficacy for off-label indications, diminished prescribing rates. Conversely, prescriptions filled at U.S. pharmacies continued to rise. Gabapentin increased by 55% from 2012 to 2016 and in 2017 was one of the top ten most dispensed drugs at U.S. pharmacies (Goodman, 2017; Institue, 2017).

Gabapentin is now being promoted by the Centers for Disease Control and Prevention as a "safer" alternative to opioids (CDC, 2016; Dowell, 2016). In addition, The American Pain Society is recommending gabapentin be considered for post-operative pain management (Chou, 2016). It should be noted that although gabapentin has been shown to reduce total postoperative morphine consumption there is no current evidence that it reduces postoperative pain (Martinez 2017; Morrison, 2017). As increased scrutiny and regulatory requirements for opioid prescribing continues, (ex. limits for first time opioid prescriptions for acute pain) gabapentin appears to be growing in popularity as an alternative option.

2.3.3 Overview of Pregabalin

Pfizer released pregabalin under the brand name Lyrica in 2005, one year after its predecessor gabapentin became available in generic formulations. Pregabalin has a greater bioavailability than gabapentin and is estimated to be three to ten times as potent. (Lauria-Horner, 2003). The FDA approved Lyrica for the treatment of epilepsy, neuropathic pain following shingles, diabetic nerve pain, and fibromyalgia. However, similar to gabapentin, much of its use is for to off-label indications (Giladi, 2015). The most common off-label uses of Lyrica include chronic pain (most often back pain) and generalized anxiety. There is little evidence that pregabalin is effective in the treatment of chronic lower back pain and significant adverse events have been reported including, dizziness, mental confusion, fatigue, and visual disturbances (Shanthanna, 2017). Although medical experts are divided on their appropriate use, pregabalin has remained popular and profitable. In 2016, spending on Lyrica reached nearly %4.5 billion in USD (Goodman 2017). As Lyrica's patent expires in 2019, it can be expected to continue its rise in popularity.

2.3.4 Gabapentinoids—Literature Review on Potential for Abuse

Gabapentinoids have historically been thought to have little to no abuse or misuse potential as indicated by their FDA scheduling. Pregabalin is currently classified as a schedule V medication--indicating the lowest potential for abuse and gabapentin remains unscheduled (fda.gov). However, the potential for abuse may be greater than originally thought. A literature search on gabapentinoid abuse

and misuse was conducted using key resource databases including PubMed, WebofScience, and EBSCOhost. Search terms included: gabapentinoid, gabapentin, pregabalin, Lyrica, Neurontin, abuse, and misuse. Articles were screened for inclusion by abstract review and relevant articles were obtained in their entirety. Articles were excluded if they were not available in English. The primary focus of the review was concentrated to cohort studies; however, case studies in which gabapentinoid dependence or abuse was the primary focus were also included. A total of 28 articles were included for review. Articles were separated into 5 categories: Selected Case Studies, Surveys and Interviews, Retrospective Cohort Analysis, Toxicological Investigations, and Literature Reviews.

i. Selected Case Studies: Gabapentinoid dependence has been noted for nearly a decade. Individual case studies were reported in several countries in the years following both medications release. Withdrawal symptoms have been compared to benzodiazepines and have required hospitalization in some cases (Victorri-Vigneau, 2007; Kruszewski,2009). Similarities among case studies include a history of substance abuse and self-medicating at higher than recommended doses (Filipetto, 2010; Satish, 2012). However, there have been instances of dependence in patients with no prior history of abuse (Halaby, 2015). A summary table of the selected cases studies in shown in Table 2.4.

Table 2.4 Summary of selected case studies relating to gabapentinoid dependence, abuse, and misuse.

Study, Journal, Year	County	Major Outcomes
Victorri-Vigneau et al. Pharmacopsychiatry 2007	France	• Patient developed GBP dependence and began taking more than recommended daily dosage. • Exhibited withdrawal symptoms that required hospitalization.
Kruszewski et al. J Psychiatr Pract. 2009	USA	• Patient developed GBP dependence and began taking more than recommended daily dosage. • Withdrawal symptoms similar to benzodiazepines.
Filipetto et al. J Am Osteopath Assoc. 2010	USA	• Patient with history of opioid abuse doctor-shopping for PRG.
Reeves and Burke Prim Care Companion CNS Disorder 2014	USA	• Reported abuse of PRG and quetiapine after second arrest of driving under the influence.
Satish et al. J Neuropsychiatry Clin Neurosci. 2015	India	• GBP dependence developed in male with opioid use disorder.
Halaby et al. Curr Drug Saf. 2015	Lebanon	• Case report of female who developed PRG dependence with no history of substance misuse or abuse.

ii. Surveys and Interviews: Surveys, interviews, and questionnaires can give valuable insight into abuse trends and behavioral motivators. Gabapentin abuse was first noted in the U.S. prison system in 2004 (Reccoppa 2004). Physicians at the penitentiary began to see an

increase in requests for gabapentin. When pill counts were conducted, only 19 of 96 patients were found to be in possession of their prescribed medication. Inmates admitted to diverting their gabapentin prescriptions. Those individuals who were found in possession of the diverted medication admitted in a series of interviews to gabapentinoid abuse. Many noted previous cocaine abuse.

There would be a substantial time gap until further studies were carried out in the general public. In 2011, an investigation showed a significant increase in online content and posting by individuals on the misuse and abuse of gabapentinoids (Schifano, 2011). Several studies completed both in the U.S. and Europe found that gabapentinoid abuse was higher than previously thought. Overall, the prevalence of gabapentinoid misuse was estimated to be 1.1% for gabapentin and 0.5% for pregabalin (Vikas, 2014). However, these rates increased significantly for those with a history of substance abuse—with some estimates over 20% (Baird, 2014; Wilsens, 2014; Smith, 2016; Bastiaens, 2016). Respondents cited the ease of obtaining the medication and the potentiating effect of concomitant use as reasons for abuse (Baird, 2014; Snellgrove, 2017; Lydon, 2017). A summary table of the selected cases studies in shown in Table 2.5.

Table 2.5 Summary of survey and interview studies relating to gabapentinoid dependence, abuse, and misuse.

Study, Journal, Year	County	Major Outcomes
Reccoppa et al. Am J Addict 2004 *[n=96]*	USA	• Less than 20% of patient prescribed GBP were found to be in possession of patient prescribed GBP. • Admission GBP abuse and previous cocaine abuse noted in interviews conducted with inmates.
Schifano et al. Psychother Psychosom 2011 *[n=32 (websites)]*	International	• Increase in online content related to gabapentinoid abuse
Baird et al. Eur Addict Res. 2014 *[n=129]*	United Kingdom	• Gabapentinoid misuse in 22% of respondents. Over a third were using it concomitantly with methadone to potentiate a high.
Vikas et al. Br J Clinc Pharmacol. 2014 *[n=1500]*	United Kingdom	• Based on an internet survey prevalence estimates of misuse were determined for GBP (1.1%) and PRG (0.5%)
Wilens et al. Am J Addict. 2014 *[n=169]*	USA	• Of patients in treatment for opioid dependence, 22% and 7% reported to non-medical use of GBP and PRG respectively.
Smith et al. Am J. Psychiatry 2015 *[n=503]*	USA	• 15% of respondents with a history of drug abuse (n=503) reported GBP use to "get high"--a 2950% increase from 2008. • Respondents were current non-medial users of opioids
Bastiaens et al. Psychiatr Q. 2016 *[n=250]*	USA	• Individuals in a correctional institution with a previous history of substance abuse were asked about past drug use.

		• Of those with an opioid use disorder 26% reported to missing GBP compared to 4% without an opiate use disorder.
Snellgrove et al. CNS Drugs 2017 *[n=256]*	Germany	• Respondents were in treatment for past illicit drug use • 56% had used PRG with most obtaining it illegally.
Lyndon et al Addiction 2017 *[n=30]*	United Kingdom	• Questionnaire revealed PRG was easy to obtain by heroin users and used concomitantly due to its reinforcing effects.

iii. Retrospective Cohort Analysis:

A majority of studies utilizing a retrospective cohort design focused on two main areas: (1) gabapentinoid prescriptions administered at higher than recommended doses and (2) drug related overdose fatalities involving a gabapentinoid.

Pregabalin was found to have higher prevalence in post mortem analysis of drug overdose fatalities (Hakkinen, 2014; Chiappini and Schifano, 2016; Haukka, 2017). Rates appear to be rising, with one study finding that over 75% of fatalities occurred in the past four years (Chiappini and Schifano, 2016). Increased prescribing rates was strongly associated with increased overdose fatalities (Lyndon, 2017). In addition, concomitant opioid use was associated with an increased risk of fatality of over 40% (Gomes, 2017).

Gabapentinoids were often prescribed in higher than recommended doses. Broden et al. found that 8.5% of all pregabalin prescriptions written in Sweden

from 2006 to 2009 exceeded maximum recommended doses (Broden, 2014). A study conducted in the U.S. found that the top 1% of gabapentin prescriptions were three times the recommended daily dosage (Peckham, 2017).

A major gap in literature is that nearly all retrospective cohort studies were carried out in Europe. The United States unique health care system makes it difficult to extrapolate trends and findings. This is an area in which continued research is needed to understand the implications to the U.S. population. A summary table of the selected cases studies in shown in Table 2.6.

Table 2.6 Summary of retrospective cohort studies relating to gabapentinoid Dependence, Abuse, and Misuse.

Study, Journal, Year	**County**	**Major Outcomes**
Boden et al. Eur J Clinc Phamcol 2014 *[n=48,550]*	Sweden	• 8.5 % of all pregabalin prescriptions dispensed from July 2006 and December 2009 exceeded maximum recommended dosages. • Risk factors for receiving a higher than recommended dosage include: gender (male), previous history of substance use disorder, income, epilepsy, and previous high doses of other drugs with potential for abuse.
Hakkinen et al. Forensic Sci Int 2014 *[n=13,766]*	Finland	• PRG and GBP found in 315 and 43 overdose deaths from 2010-2011 in Finland. • In 48.1% of PRG cases and 18.6% of GBP cases, drug abuse was associated.
Chiappini and Schifano	Europe	• During the investigation period (GBP: 2004-2015; PRG: 2006-2015)

CNS Drugs 2016 *[n=115,616 (PRG)]* *[n=90,166 (GBP)]*		27 and 86 fatalities were associated with GBP and PRG respectively. 75% of reported OD fatalities were within last 4 years of study.
Bossard et al. Clin Drug Investig 2016	France	• No significant association between drug abuse and PRG exposure was found.
Gomes et al. PLoS Med 2017 *[n=184,310]*	Canada	• Concomitant treatment of opioids with GBP increases the risk of fatal opioid overdose death. (adjusted odds ratio: 1.49) • >40% of individuals who received a GBP prescription in the previous year also received an opioid prescription.
Peckham et al. Clin Drug Investig. 2017 [n=4,366,019]	USA	• Top 1% of GBP users filled prescriptions for a mean dose of >12,000 mg/day--three time more than the recommended maximum dosage.
Lyndon et al. Addiction 2017. *[n=unspecified]*	United Kingdom	• Number over overdose death climbed from <1 to 137 from 2009 to 2015. An opioid was involved in >75% of deaths. • Increased deaths were highly correlated with prescribing (R^2 = 0.94; an increase of 100,000 prescriptions was associated with a 5% increase in overdose deaths).
Haukka et al. Addiction 2018 *[n=2974]*	Finland	• Of the psychoactive drugs investigated, PRG was present in 37% of cases. • Fatal overdose was estimated to be 4 times higher in non-medical use of PRG. • 21 of 30 interviewees had experience with self-administering PRG mainly due to its enhancement of euphoric effect.

iv. Toxicological Investigations: Several studies have investigated the prevalence of gabapentinoids, specifically pregabalin, in toxicology testing. In patients currently in treatment, or with a history of an opioid use disorder, rates of a positive pregabalin test without a prescription ranged from 7% to 12.1% (Grosshans, 2013; McNamara, 2015; Smellgrove, 2017). Notably, all studies investigating toxicological data were conducted in Europe. The studies are summarized below in Table 2.7.

Table 2.7 Summary of toxicological studies relating to gabapentinoid Dependence, Abuse, and Misuse.

Study, Journal, Year	County	Major Outcomes
Grosshans et al. Eur J Clin Pharmacol 2013 *[n=124]*	Germany	• 12.1% of toxicology tests on patients with opiate dependency resulted in a PRG positive test
McNamara et al. Ir Med J. 2015 *[n=440]*	Ireland	• 7% of individuals on opioid substitution therapy tested positive for PRG without a prescription.
Snellgrove et al. CNS Drugs. 2017 *[n=253]*	Germany	• 13% of urine samples were positive for PRG.

v. Literature Reviews: Four literature reviews on gabapentinoid abuse, misuse, and dependence were identified. All have been published in the last five years. The authors unanimously report that individuals with a

prior history of abuse are particularly vulnerable to gabapentinoids, specifically pregabalin. Concern was raised over the validity of the clinical trials, that often exclude individuals with a previous history of substance abuse, perhaps leading to an underestimation of the potential for addiction to these medications. A summary table of the selected literature review is in shown in Table 2.8.

Table 2.8 Summary of literature reviews relating to gabapentinoid Dependence, Abuse, and Misuse.

Study, Journal, Year	County	Major Outcomes
Schifano CNS Drugs 2014 *[n=29]*	International	• Increasing reports of gabapentinoid abuse and misuse particularly in individuals with substance abuse history.
Schjerning et al. CNS Drugs 2016 *[n=58]*	International	• Continued reports of possible PRG abuse. Clinical trials note common side effect of euphoria. Individuals with history of opioid abuse particularly vulnerable.
Evoy et al. Drugs 2017 *[n=59]*	International	• Comprehensive findings relating to gabapentinoid abuse. • Found increasing evidence of the potential for abuse of Gabapentinoids particularly in individuals with a history of opioids abuse.

Bonnet and Scherbaum European Neuropsychopharmacology 2017 *[n=106]*	International	• Authors conclude that GBP has limited addictive qualities. PRG has slightly higher potential for addiction. Individuals with a history of substance use disorders may be particularly vulnerable for misuse.

This literature review demonstrates the rising concern over the safety of gabapentinoids. In 2014, as a response to the growing number of filled prescriptions, England's Department of Health released a memo to prescribers of gabapentinoids alerting them to the potential for abuse and diversion. (NHS England 2014). Deaths involving a gabapentinoid had increased from 0 in 2008 to over 150 in 2016, with 80% of them involving an opioid (U. of Bristol, 2017). Studies shown that concomitant use of an opioid and gabapentinoid may create an additive effect leading to increased respiratory depression (Lyndon, 2017). Pregabalin may have an even higher potential for abuse due to its higher bioavailability and subsequent potency.

2.3.5 Literature Gap

These literature trends show a growing body of evidence on the potential for the abuse and misuse of gabapentinoids. However, there is little literature describing the prescribing patterns for these two medications. Due to gabapentin and pregabalin being off or low on the DEA scheduling list, they are not traditionally tracked by prescription drug monitoring programs leading to a

particularly large knowledge gap. In addition, most retrospective cohort studies and investigations involving toxicological data were not documented in the U.S. As these medications continued to rise in popularity, understanding how they are being prescribed within the U.S. is critical to understanding potential risk factors, and, hence, potential points of intervention.

2.4 Research Framework

Subsection 2.4 outlines the conceptual model utilized for the research framework of this dissertation. A summary of the chosen model (The Andersen Healthcare Utilization Model) is first presented. Next, an overview of the predisposing, enabling, and need characteristic relevant to this analysis is detailed. Finally, a schematic of the final model is presented.

2.4.1 The Andersen Healthcare Utilization Model

The research framework utilized for this study was derived from on The Andersen Healthcare Utilization Model. Andersen theorizes that healthcare utilization is driven by three major categories of influencing characteristics: predisposing, enabling, and need (Andersen and Aday 1974, Andersen 2008). Predisposing characteristics are individual level determinants that influence a patients decision to utilize healthcare services. These include socio-demographic variables such as age, race and gender. Enabling resources describe the "means" or availability an individual may have for healthcare access and utilization. These include economic contributors such as income and health insurance status. Need factors describe a patients necessity for healthcare, including evaluated and

perceived need, that motivate an individual to seek care. Need factors can include individual-level characteristics such as severity of illness and comorbidities, in addition to population-level health status.

The three major categories described in Andersen's model all lead to differences in health behaviors and utilization that ultimately impact health outcomes. By considering each category in this dissertation, a comprehensive understanding of the factors which most strongly influence gabapentinoid utilization, coprescribing of a gabapentinoid and an opioid, and impact on opioid overdose can be determined.

2.4.2 Predisposing, Enabling, and Need Characteristics

The population risk factors outlined in Chapter 2.2 drove the selection of predisposing, enabling, and need characteristics for thus study and are summarized here.

Predisposing Characteristics

Predisposing characteristics used for the model include sex, race, and age. Although men are more likely to suffer from an overdose death, women are more likely to report cravings and may be more susceptible to addiction (KFF, 2017; Kaplovitchch, 2015; Cochran, 2014; Back, 2011). Thus, each sex has its own unique set of risk behaviors. Non-Hispanic whites are significantly more likely to be prescribed opioids and also more often likely report to their misuse or abuse (Liebshult, 2010; Fleming, 2007; Olsen, 2006, Pletcher, 2008). Historically, increased age is associated with

a decreased likelihood of opioids abuse or non-medical use, however this trend has been shifting in recent years. Notably, fatal overdoses in the 55+ population has nearly doubled in a decade (KFF, 2017).

Enabling Characteristics

Enabling characteristics are described as facilitating the utilization of health services. Traditionally, health insurance status is a key enabling characteristic. Although the cohort consists of all Medicaid beneficiaries, nuances within the Medicaid program may impact gabapentinoid utilization.

The qualifying category is the broad categorial eligibility criteria under which the beneficiary is applying for or receiving assistance. Common criteria for eligibility include individuals with a disability and families with dependent children. The payment category indicates a more specific coverage group that the beneficiary is applying for or receiving assistance. Common payment categories include low income families, individuals that qualify through supplemental security income, and persons that are aged, blind, or disabled. Notably, individuals with disabilities are indicated in both the payment and qualifying categories. The disabled population is both more likely to receive an opioid and suffer from an overdose event (Florence, Zhou, Luo, & Xu, 2016; Meara et al., 2016).

In addition to the eligibility criteria the patient may qualify for, the type of plan the individual is enrolled-in may differ. Patients in health maintenance organizations have been shown to be less likely to receive an

opioid prescription(Olsen, Daumit, & Ford, 2006). The type of plan (source) was included in this model to determine if this trend held true for gabapentinoid and opioid co-prescribing. Physician-level influences including physician specialty and type variation also operate as enabling characteristics but unfortunately, were not included in the data set and therefore could not be included in the analysis.

Need Characteristics

Need characteristics were assessed by conditions which are often diagnosed when either an opioid or gabapentinoid would be likely prescribed. These include fibromyalgia, diabetic peripheral nerve pain, seizure, restless syndrome, and chronic pain. In addition, mental health disorders were also included due to their high comorbidity rate with opioid abuse diagnoses (Dufour, 2014; Cochran, 2014; Barth, 2008; White, 2009).

Health Behaviors

The predisposing, enabling, and need characteristics outlined above all play an important role in influencing health behaviors. The primary health behavior investigated in this dissertation was prescription utilization. Prescription utilization encompassed a broad range of prescribing characteristic including type, potency, length of use, and concomitant administration. Research shows that prescribing characteristics often lead to an increased likelihood of prescription misuse that may develop into

continued drug-seeking behavior and adverse drug events (Liang, 2009; Bohnert, 2011; Buamblatt, 2014; Edlund 2014; White 2009).

Opioid abuse was also included in the health behavior section of this model. The growing body of literature on gabapentinoids abuse, presented in Chapter 2, suggests that individuals with a history of opioid abuse are particularly susceptible to abuse or misuse of gabapentinoids. Although opioid abuse can also be classified as a health outcome, in this model only a history of opioid abuse (not new events based on prescribing) was used as a possible predictor of additional health behaviors and outcomes. Therefore, it was included as a health behavior that may influence prescribing patterns and overdose events.

Health Outcomes

As a whole, the Andersen Health Utilization model utilized for this dissertation is an attempt to frame individual level characteristics that may influence behaviors and ultimately health outcomes. The primary focus of Aim 4 is the outcome of opioid overdose based on the predisposing, need, enabling characteristics defined above in addition to health behaviors. Based on the growing body of literature indicating the potentiating effect of gabapentinoids on the euphoric effects, as well as the potential that gabapentinoids have to further induce respiratory depression, gabapentinoid utilization may indeed be significantly associated with overdose events (Baird, 2014; Snellgrove, 2017; Lydon, 2017).

A modified version of Andersen's framework based on the work of this study is shown in Figure 2.2. Additional characteristics not outlined above could be important driving factors of health care utilization. Notably, health care beliefs, family dynamics, and perceived need being among them. These characteristics are included in the framework, although they cannot be directly measured in this study. All measurable characteristics are indicated on the figure in bold.

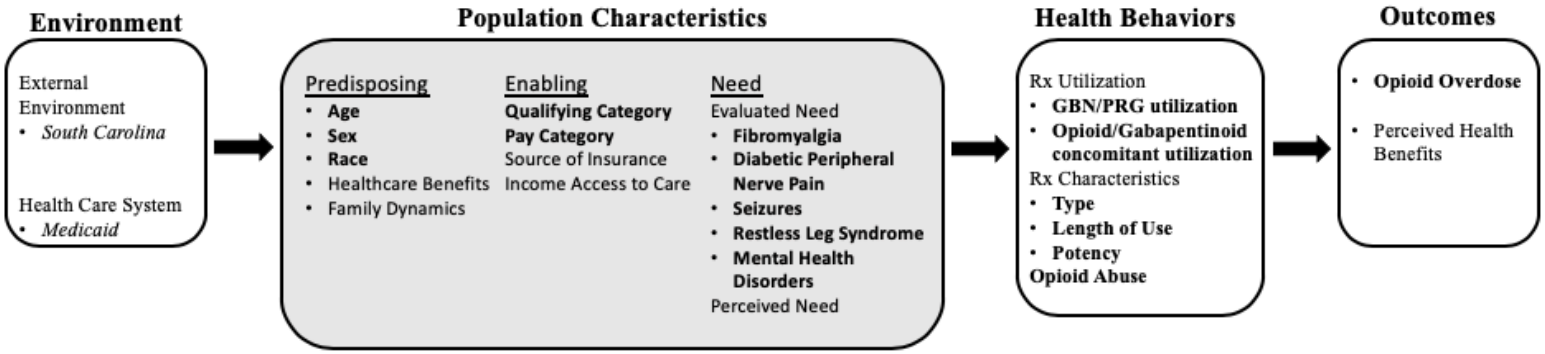

Figure 2.2 A modified version of Andersen's framework based on the work of this study.

CHAPTER 3

METHODOLOGY

This chapter describes in detail the methodology utilized to achieve the aims of this study. The chapter first outlines the project overview and rationale, followed by a restatement of aims. The study design, data source, and inclusion and exclusion criteria for the final cohort by aim is then described. Additionally, a thorough explanation of the data files and variables used for analysis is included. Finally, the data analytic plan for each aim of the investigation is laid out with summarizing tables. SAS software version 9.3 was used for all statistical analyses and computations outlined in this chapter.

3.1 Project Overview and Rationale

This study aims to describe trends in the prescribing of gabapentinoids, specifically gabapentin and pregabalin. The analysis will investigate demographic variances, prescription utilization, co-prescribing rates, and potential predictors of the concomitant prescribing of a gabapentinoid and an opioid and subsequent adverse events. It is clear from the literature that growing concern is mounting on the potential for gabapentinoid misuse, especially in individuals with a history of substance abuse. This is especially troubling, as these drugs are now being recommended as safer alternatives to opioids and may indeed be prescribed to those patients at highest risk for developing addiction. In addition, it is believed

that the co-prescribing of a gabapentinoid and an opioid puts the user at increased risk for overdose and adverse drug events which will be further investigated here. Even among these growing concerns, gabapentinoid prescriptions filled at U.S. pharmacies continue to rise. South Carolina residents may be at higher odds of the co-prescribing of opioids and gabapentinoids, as the state is currently 9th in overall opioid prescribing nationally. In addition, Medicaid recipients are more likely to receive an opioid prescription, making this population particularly at risk. Yet, there is little understanding of gabapentinoid prescribing patterns. Understanding how these prescriptions are being utilized is of crucial importance as it will help identify at risk populations for targeted intervention in South Carolina. In addition, it will give further insight into the potential for adverse events from these medications.

3.1.1 Restatement of Aims

The objective of this study is to conduct a retrospective cohort study of South Carolina's Medicaid population to determine the following:

- Aim 1: To identify prescribing patterns of gabapentinoids including variances in type, dosage, length of prescription, and population demographics.
- Aim 2: To determine rates and trends of gabapentinoid and opioid co-prescribing.
- Aim 3: To investigate predictive factors associated with an increased likelihood of gabapentinoid and opioid co-prescribing.

- Aim 4: To determine possible association between emergency department visits for opioid overdose and gabapentinoid and opioid co-prescribing.

3.2 Data Source

3.2.1 Medicaid and Opioid Prescribing

As outlined above, South Carolina's Medicaid population may be particularly at risk to increased rates of gabapentinoid and opioid co-prescribing. South Carolina practitioners write nearly 5 million opioid prescriptions per year—ranking 9th in the country for overall prescriptions filled at U.S. pharmacies (CDC, 2017; DHEC, 2017). Medicaid beneficiaries account for a disproportionate number of opioid prescriptions, with one in four Medicaid beneficiaries having filled at least one opioid prescription within the last 360 days (ExpressScripts, 2016). Nearly a third are additionally co-prescribed a benzodiazepine or muscle relaxer. Prescription overdose fatalities are up 18% from 2014 and utilization at state-run substance abuse treatment centers is up 135% (DHEC, 2018; DAODA, 2017). For these reasons, South Carolina Medicaid data was selected as the best choice for analysis as the purpose of this study was to investigate a population particularly at risk. In addition, Medicaid data gives a unique opportunity due to its extensiveness in reporting allowing a wide array of patient-level variables to be investigated.

Specifically, South Carolina Medicaid data obtained from The Office of Revenue and Fiscal Affairs (RFA), years 2009-2016, are utilized for this

investigation. Changes in South Carolina's PDMP program, SCRIPTS, determined the inclusion years. SCRIPTS was implemented statewide in 2008. 2009 was chosen as the initial year included for this study to ensure physicians were adequately trained and educated on the program during the initial year of implementation. In 2017, state law mandated that providers prescribing CS II-IV medications must check SCRIPTS for all federally insured patients. It is likely that this mandate may impact prescribing behaviors and therefore 2017 was excluded to avoid confounding variables. Once additional data becomes available, future work should include an investigation to determine if the newly implemented SCRIPTS mandate has impacted prescribing behaviors.

3.2.2 South Carolina Medicaid Overview

South Carolina's Medicaid program, known as Healthy Connections, is a major source of healthcare for low income individuals and those with disabilities in South Carolina. Healthy Connections is administered by the South Carolina Department of Health and Human Services (SCDHHS) and is funded through a combination of state and federal tax money (SCDHHS, 2018). South Carolina remains one of 19 states to opt-out of Medicaid expansion (KKF, 2017). Even without expansion, enrollment has continued to rise, up over 20% from 2013 to 2016 (SC Health Viz, 2016). Over 1 million beneficiaries--nearly one in four South Carolinians--are enrolled annually. In 2016, 64,678 adults ages 18-64 enrolled in Medicaid, accounting for 30.6% of enrollees (SC Health Viz, 2016).

3.2.3 Medicaid Eligibility

To qualify for Medicaid in South Carolina, an individual must meet strict eligibility requirements. In general, enrollees must be a U.S. citizen, legal alien or permanent resident and have low income or a disability. Currently, Medicaid coverage in South Carolina is not available for non-disabled adults with no dependents, regardless of income. For individuals that do qualify, income requirements vary based on a variety of factors including pregnancy and number of dependents. The current maximum income limit for a family of four is $32,319 (benefits.gov, 2018). Due to changes in health status and income throughout the year, individuals may fall in and out of eligibility.

3.2.4 South Carolina Medicaid Benefits

South Carolina Medicaid covers a variety of medically necessary services. These include doctor office visits and family planning services, in addition to hospital inpatient, outpatient and emergency room visits. For adults, a physical once every two years is covered. Laboratory and x-ray services are additionally covered. Medicaid also covers alcohol and drug abuse services and some behavioral health services. Copayments are generally less than $4.00. Prescriptions are covered; however, similar to other insurance plans, coverage is not guaranteed for all medications and some require prior authorization. Generic gabapentin is currently covered by South Carolina Medicaid as a preferred drug, while the non-generic Lyrica (pregabalin) requires preauthorization.

Transportation assistance for non-emergency visits is also provided to and from appointments.

3.3 Cohort

The South Carolina Medicaid data obtained from the RFA was specific for this study. Data was provided only for individuals ages 18-64 at any point from January 1, 2009 to December 31, 2016 who filled at least one prescription for a gabapentinoid or an opioid. Dual eligible beneficiates were not included in the dataset provided.

The cohort for Aim 1 was restricted to adult Medicaid beneficiaries between the ages of 18 and 64 residing in the state of South Carolina who filled at least one prescription for a *gabapentinoid* between January 1, 2009 and December 31, 2016. Individuals who received a gabapentinoid prescription, regardless of total length of Medicaid enrollment, were included to ensure a full accounting of all gabapentinoid prescriptions covered by Medicaid throughout the study period.

The cohort for Aim 2 was restricted to adult Medicaid beneficiaries between the ages of 18 and 64 residing in the state of South Carolina who filled at least one prescription for an *opioid* between January 1, 2009 and December 31, 2016. Further analysis for this cohort included patients that had at least 1 day of overlapped administration of a gabapentinoid and opioid prescription. Patients prescribed buprenorphine and methadone were not included in the opioid analysis portion of Aim 2 due their utilization in medication assistance substance abuse treatment due to the likely difference in prescribing behaviors for this population.

The cohort from Aim 1 was used as the base of analysis for Aim 3. In addition, patients must have been continuously enrolled in SC Medicaid for the 12 months prior to the first prescribing event. Furthermore, patients with a diagnosis of cancer pain at any time throughout the study period were excluded from analysis due to variances in prescribing patterns for individuals with cancer diagnoses. The first prescribing event was defined as the pharmacy date for the first concomitant prescription of either an opioid or gabapentin. If the patient had no overlap in prescribing throughout the study period, the pharmacy date for the first *gabapentinoid* prescription was used. Patients prescribed an opioid only, with no concomitant gabapentinoid utilization, were not included in this analysis.

The cohort from Aim 2 was used for the base of analysis for Aim 4. In addition, patients must have been continuously enrolled in SC Medicaid for the 12 months prior to and 12 months following the first prescribing event. Similar to the cohort for Aim 3, patients with a diagnosis of cancer pain at any time throughout the study period were excluded from analysis. The first prescribing event was defined as the pharmacy date for the first concomitant prescription of either an opioid or gabapentin. If the patient had no overlap in prescribing throughout the study period, the pharmacy date for the first *opioid* prescription was used. Patients prescribed a gabapentinoid only, with no concomitant opioid utilization, were not included in this analysis. Figure 3.1 outlines the cohort selection criteria by Aim.

3.4 Medicaid Data Files

The following Medicaid files were utilized during this investigation: Recipient Files, Health Insurance Claim (HIC) Files, Inpatient and Outpatient Hospital Files, and Pharmacy Files.

i. Recipient Files: Recipient files contain data on recipient characteristics. They contain an encrypted recipient ID which can be utilized to link patients across additional Medicaid files. This is the main file that contains information on patient demographics including race and sex. The files also contain data on eligibility status and Medicaid recipient category.

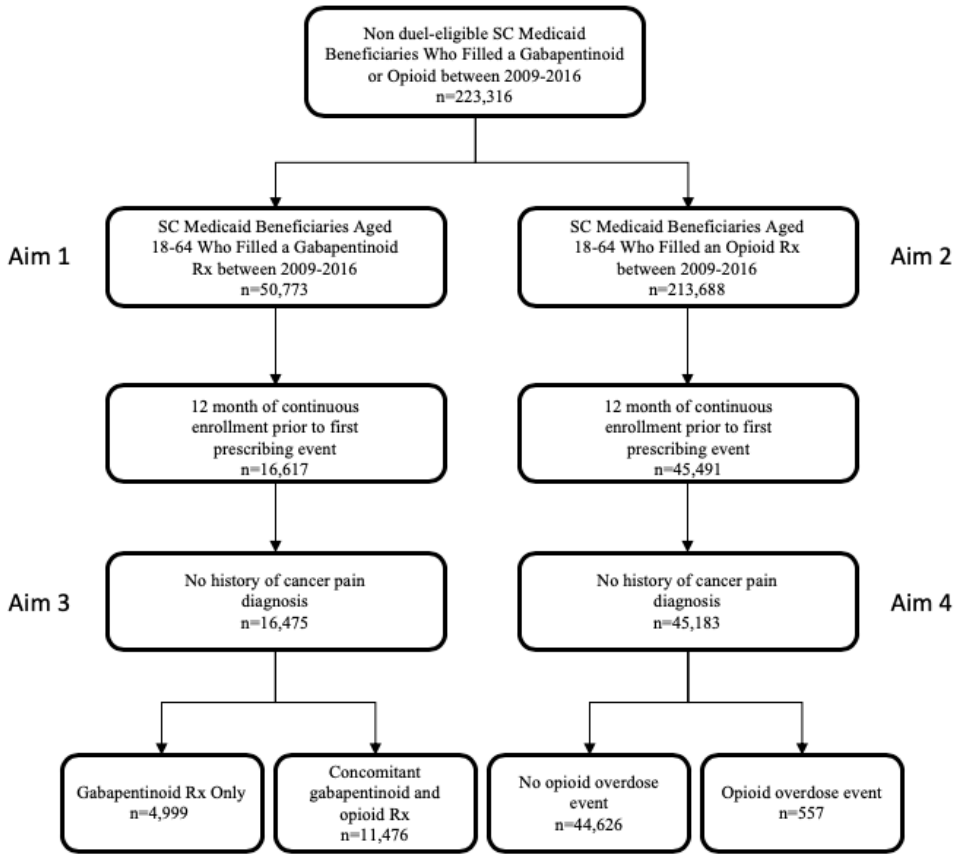

Figure 3.1 Selection criteria by Aim.

ii. Health Insurance Claim (HIC) Files: HIC files contain data on services provided outside of a hospital setting. These files contain information such as month and year of the provided services, location of the service, CPT codes, and diagnosis codes. In addition, economic information is provided such as the charges and amount paid for a visit.

iii. Inpatient and Outpatient Hospital Files: Inpatient and outpatient hospital files provide information specific to hospital visits. The data contained in these files includes CPT codes, diagnosis codes, and covered charges and amount paid, which are similar to those variables provided in the HIC files. Additionally, these files contain ER specific information such as admission source, category of service, and ER flag.

iv. Pharmacy Files: Pharmacy files include detailed information on all filled prescription medications by Medicaid beneficiaries. Specifically, the files contain information on the medication including national drug codes, drug indicator, therapeutic class, quantity dispensed, days supplied, and number of refills. The month and year the medication was dispensed in addition to charges and amount paid are also provided.

In this study, individuals were linked across files by encrypted recipient ID. Prescription files from the Medicaid pharmacy records were utilized as the main outcomes measures for Aims 1-3. The main outcome for Aim 4 utilized hospital ED visits due to opioid overdose which are found in the Inpatient and Outpatient

Hospital Files. Gabapentinoid and opioid prescriptions were identified through National Drug Codes (NDCs). ED visits due to opioid overdose were identified through ICD-9 and ICD-10 codes. Table 3.1 shows variables included in each file type used for this analysis.

3.5 Variables

3.5.1 Dependent Variables

The primary dependent variable used for this study was a filled prescription for a gabapentinoid or opioid. This variable served as the basis for the overall cohort and what all other aims built upon. For aims 2 and 3, both gabapentinoid and opioid prescription were used to identify concomitant opioid and gabapentinoid utilization. Medications were identified by the 11-digit National Drug Code (NDC) code found in the Medicaid pharmacy file. An NDC is a unique identifier which can be found on the drug packaging and is assigned by the FDA. The code gives key information on the manufacturer, product, and packaging. NDC codes were obtained from the National Drug Code Directory found on the US FDA website.

Visits to the ED for opioid overdose was the main outcomes measure investigated in Aim 4. Drug overdose ED visits were identified by ICD-9 or ICD-10 diagnosis codes in the Medicaid Inpatient and Outpatient Hospital Files. An overdose indication in the primary or secondary diagnosis fields was included for analysis.

Table 3.1 List of Variables Included in Analysis

Variable Category	Variable Name	Variable Description
Recipient File	Encrypted Recipient ID	Used as primary key for recipient linking
	Dual Eligibility Indicator	0=No; 1=Yes
	Month/Year of Eligibility & Ineligibility Dates	MonYY5
	Qualifying Category	0=Disabled; 1=AFDC; 2=Other
	Pay Category	0=Low Income Families; 1=SSI; 2=Aged, Blind or Disabled; 3=Other
	Source	0=FFS; 1=HMO
	Race	0=White; 1=Black; 2=Hispanic; 3=Other
	Sex	0=Male; 2=Female
Health Insurance Claim Files (HIC)	Encrypted Recipient ID	Used as primary key for recipient linking
	Month/Year of admission date	MonYY5
	Age in Year	Patient age in years collapsed into age categories
	Primary Diagnosis	ICD-9 and ICD-10 diagnosis codes
	Secondary Diagnosis	ICD-9 and ICD-10 diagnosis codes
Inpatient and Outpatient Hospital Files	Encrypted Recipient ID	Used as primary key for recipient linking
	Month/Year of admission date	MonYY5
	Age in Year	Patient age in years collapsed into age categories
	Primary Diagnosis	ICD-9 and ICD-10 diagnosis codes
	Secondary Diagnosis	ICD-9 and ICD-10 diagnosis codes
Pharmacy Files	Encrypted Recipient ID	Used as primary key for recipient linking
	Month/year date dispensed	MonYY5
	Age in Year	Patient age in years collapsed into age categories
	NDC & Drug Name	Unique drug code and name
	Quantity	Integer: number of pills dispensed
	Refills	Integer: Number of refills remaining
	Days supplied	Integer: Number of days supplied

Table 3.2 outlines the dependent variable for each aim. A complete list of ICD-9 and ICD-10 codes used for ED visits for opioid overdose are found in Table 3.3.

Table 3.2 Dependent variables to be used in statistical analysis.

Aim	Variable Name	Type	Description
1	Gabapentinoid Rx Fill	Dichotomous	0=no; 1=yes
2,3	Concomitant Opioid and Gabapentinoid Rx Utilization	Dichotomous	0=no; 1=yes
4	Visit to ED for OD	Dichotomous	0=no; 1=yes

Table 3.3 ICD-9 and ICD-10 codes used to identify ED visits due to Opioid Overdose

	ICD-9 Codes	ICD-10 Codes	
Drug Poisoning	96500	T400X1A	T403X4A
	96501	T400X1D	T403X4D
	96502	T400X1S	T403X4S
	96509	T400X4A	T404X1A
	9701	T400X4D	T404X1D
	E8500	T400X4S	T404X1S
	E8501	T401X1A	T404X4A
	E8502	T401X1D	T404X4D
		T401X1S	T404X4S
		T401X4A	T40601A
		T401X4D	T40601D
		T401X4S	T40601S
		T402X1A	T40604A
		T402X1D	T40604D
		T402X1S	T40604S
		T402X4A	T40691A
		T402X4D	T40691D
		T402X4S	T40691S
		T403X1A	T40694A
		T403X1D	T40694D
		T403X1S	T40694S

Sources: HCUP Case Study--Exploring How Opioid-Related Diagnosis Codes Translate from ICD-9-CM to ICD10-CM; CDC Guide to ICD-9 and ICD-10 Codes Related to Poisoning and Pain

3.5.2 Key Explanatory Variables

Prescription Characteristics

Differences in type, dose, and length of use of a gabapentinoid prescription are predicted to explain significant variation in co-prescribing rates and likelihood of ED visit for overdose. All three variables were derived from the Medicaid pharmacy file. The type of gabapentinoid (gabapentin or pregabalin) was identified by the NDC code. Dosages were provided in milligrams. Days supplied was provided in day increments.

To assess comparative daily potency, daily dosages were calculated for both gabapentinoids and opioids. In general, daily dosages are calculated by multiplying the number of times the medication is administered per day by the potency. Opioid potency per milligram varies widely based on the medication (ie. Morphine vs Oxycodone) and mode of administration (ie. sublingual vs transdermal). It is customary when comparing opioids to utilize a morphine equivalency conversion factor, often referred to as the Morphine Equivalent Daily Dosage (MEDD). The MEDD was subsequently calculated for all opioid prescription identified in this analysis. A full list of opioids included in this analysis as well their conversion factors are listed in Table 3.4.

A gabapentinoid equivalency conversion has not been established and therefore a traditional daily potency has been used--referred to for this study as Gabapentin Daily Dosage (GDD). In general, pregabalin will have observed lower daily doses. However, due to a higher potency, even at lower dosages it is

considered the 'stronger' medication. For this reason, these medications have been stratified for most analyses. The dosing calculations for GDD and MEDD are shown in Figure 3.2.

Table 3.4 Opioid Conversion Factors

Opioid	**Conversion Factor**
Codeine	0.15
Dihydrocodeine	0.25
Fentanyl	
Buccal, sublingual or lozenge	0.13
Film or oral spray	0.18
Nasal Spray	0.16
Transdermal	2.4
Hydrocodone	1
Hydromorphone	4
Levorphanol	1
Meperidine	0.1
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Pentazocine	0.37
Propoxyphene	0.23
Tapentadol	0.4
Tramadol	0.1

GDD is calculated as:

$$GDD = \frac{(quantity\ supplied) * (dose)}{(days\ supplied)}$$

MEDD is calculated as:

$$MED = \frac{(quantity\ supplied) * (drug\ strength) * (unique\ opoid\ conversion\ factor)}{(days\ supplied)}$$

Figure 3.2 Daily dosage calculations for Gabapentinoid and Opioid Prescriptions

Clinical Indications

A history of the clinical indications outlined in the research framework (based on Andersen's Model of Health Service Utilization) were included as key explanatory variables for Aims 3 and 4. These include fibromyalgia, diabetic peripheral nerve pain, seizures, restless leg syndrome, chronic pain, mental health disorders, and opioid abuse. A prior history of opioid overdose was included as a key explanatory variable in Aim 3 (as opposed to the outcome measure in Aim 4).

History of each clinical indication was collapsed into a dichotomous variable. If an ICD-9 or ICD-10 diagnosis was present for an indication prior to the first gabapentinoid prescribing event in the primary or secondary diagnosis fields, a '1' was indicated. No prior history of the diagnosis (0) was defined as the reference category. A list of all ICD-9 and ICD-10 codes for each indication are found in Table 3.5.

Table 3.5 ICD-9 and ICD-10 codes used to identify history of clinical indications

	ICD-9 Codes	**ICD-10 Codes**
Fibromyalgia	7291	M797
Diabetic Peripheral Nerve Pain	250.60, 357.20	E0940, E1040, E1140, E1240, E1340
Seizures	345.00, 345.01, 345.10, 345.11, 345.30, 345.40, 345.41, 345.50, 345.51, 345.70, 345.71, 345.80, 345.1, 345.90, 345.91, 780.31, 780.32, 780.33	G40101, G40109, G40111, G40119, G40209, G40201, G40211, G40219, G40301, G40309, G40311, G40319, G40409, G40411, G40419, G40801, G40802, G40803, G40804, G40811, G40812, G40813, G40814, G40901,

		G40909, G40911, G40919, G40A01, G40A09, G40A11, G40A19, G40B01, G40B09, G40B11, G40B19, P90, R5600, R5601, R561,
Restless Leg Syndrome	333.94	G25.81
Chronic Pain	338.21, 338.22, 338.28, 338.29, 338.0, 338.4	G89.0, G89.21, G89.28, G89.29, G89.4, G589.2
Mental Health Disorder		
• Anxiety	29384, 30000, 30001, 30002, 30009, 30010, 30020, 30021, 30022, 30023, 30029, 3003, 3005, 30089, 3009, 3080, 3081, 3082, 3083, 3084, 3089, 30981, 3130, 3131, 31321, 31322, 3133, 31382, 31382	F064, F4000, F4001, F4002, F4010, F4011, F40210, F40218, F40220, F40228, F40230, F40231, F40232, F40233, F40240, F40241, F40242, F40243, F40248, F40290, F40291, F40298, F408, F409, F410, F411, F413, F418, F419, F42, F422, F423, F424, F428, F429, F430, F4310, F4311, F4312, F488, F489, R452, R453, R454, R455, R456, R457, R4581, R4582, R4583, R4584
• Mood Disorder	29383, 29600, 29601, 29602, 29603, 29604, 29605, 29606, 29610, 29611, 29612, 29613, 29614, 29615, 29616, 29620, 29621, 29622, 29623, 29624, 29625, 29626, 29630, 29632, 29633, 29634, 29635, 29636, 29640, 29641, 29642, 29643, 29644, 29645, 29646, 29650,	F0630,F0631, F0632, F0633, F0634, F3010, F3011, F3012, F3013, F302, F303, F304, F308, F309, F310, F3110, F3111, F3112, F3113, F312, F3130, F3131, F3132, F314, F315, F3160, F3161, F3162, F3163, F3164, F3170, F3171, F3172, F3173, F3174, F3175,

	29651, 29652, 29653, 29654, 29655, 29656, 29660, 29661, 29662, 29663, 29664, 29665, 29666, 29667, 29680, 29681, 29682, 29689, 29690, 29699, 3004, 311	F3176, F3177, F3178, F3181, F3189, F319, F320, F321, F322, F323, F324, F325, F328, F3281, F3289, F329, F330, F331, F332, F333, F3340, F3341, F3342, F338, F339, F340, F341, F348, F3481, F3489, F349, F39, R4586,
• Personality Disorder	3010, 30110, 30111, 30112, 30113, 30120, 30121, 30122, 3013, 3014, 30150, 30151, 30159, 3016, 3017, 30181, 30182, 30183, 30184, 30189, 3019	F600, F601, F602, F603, F604, F605, F606, F607, F6081, F6089, F609, F69
• Schizophrenia and other psychotic disorders	29381, 29382, 29500, 29501, 29502, 29503, 29504, 29505, 29510, 29511, 29512, 29513, 29514, 29515, 29520, 29521, 29522, 29523, 29524, 29525, 29530, 29531, 29532, 29533, 29534, 29535, 29540, 29541, 29542, 29543, 29544, 29545, 29550, 29551, 29552, 29553, 29554, 29555, 29560, 29561, 29562, 29563, 29564, 29565, 29570, 29571, 29572, 29573, 29574, 29575, 29580, 29581, 29582, 29583, 29584, 29585, 29590, 29591, 29592, 29593, 29594, 29595, 2970, 2971, 2972, 2973, 2978, 2979, 2980,	F060, F062, F200, F201, F202, F203, F205, F2081, F2089, F209, F21, F22, F23, F24, F250, F251, F258, F259, F28, F29

	2981, 2982, 2983, 2984, 2988,2989	
• Attention-deficit conduct and disruptive behavior disorders	31200, 31201, 31202, 31203, 31210, 31211, 31212, 31213, 31220, 31221, 31222, 31223, 3124, 3128, 31281, 31282, 31289, 3129, 31381, 31400, 31401, 3141, 3142, 3148,3149,	F900, F901, F902, F908, F909, F910, F911, F912, F913, F918, F919, R460, R461, R462, R463, R464, R465, R466, R467, R4681, R4689
Opioid Abuse or dependence	30550, 30551, 30552, 30400, 30401, 30402, 30470, 30471, 30472	F1110, F11120, F11121, F11122, F11129, F1114, F11150, F11151, F11159, F11181, F11182,F11188, F1119, F1120, F11220, F111221, F11222, F11229, F1123, F1124, F11250, F11251, F11259, F11281, F11282, F11288, F1129, F1190, F11920, F11921, F11922, F11929, F1193, F1194, F11950, F11951, F11959, F11981, F11982, F11988,F1199,

3.5.3 Covariates

The inclusion of independent covariates was also driven by the research framework outlined in section 3.2. Age in Years was collapsed into three categories: 18-34 (reference category), 35-49, and 50-64. Race was collapsed into four categories: White/Caucasian (reference category), Black/African American, Hispanic/Latino, or other. Sex was defined as "female" (reference category) or "male".

3.6 Statistical Analysis

3.6.1 Aim 1

The objective of Aim 1 was to investigate the prescribing patterns of gabapentinoids and investigate further the key explanatory variables and covariates identified in the research framework that may explain prescription filling behaviors. Similar to the national trends outlined in Chapter 2, it was hypothesized that gabapentinoid prescriptions filled in South Carolina pharmacies would have increased over time, with increasing average daily dosage.

Four main outcome measures were investigated for both gabapentin and pregabalin: (1) Gabapentinoid prescribing rates (to include total number of prescriptions filled, percentage of Medicaid population prescribed a gabapentinoid, and average number of prescriptions per beneficiary per year), (2) prescription characteristics (quantity, dose, supply) (3) the average GDD, and (4) the percentage of prescriptions filled for gabapentin and pregabalin in which dosages exceed daily recommended limits for the maintenance of pain indications, 1800 mg/day and 600 mg/day respectively. In addition, patient demographics that may give insight into utilization were investigated and analyzed.

To investigate Aim 1 a cross-sectional retrospective cohort analysis was conducted utilizing South Carolina Medicaid data from 2009-2016. A patient must have filled at least 1 gabapentinoid prescription during the study period to be included in the patient and prescription level analyses. NDCs were utilized to identify gabapentin and pregabalin prescriptions. The cohort was further limited

to individuals aged 18-64. All gabapentinoid prescriptions were included for patient-level demographic analyses and overall prescribing rates. For dosing analyses, entries were excluded if the indicated quantity dispensed was <1 or >1,000 due to the high probability of data entry errors. A sensitivity analysis was conducted in which exclusion criteria was based on GDD (>10,000mg/day excluded). No significant differences were observed therefore the exclusion criteria based on quantity was utilized. For individual level analysis, the first prescribing event during the study period for each patient was used for the statistical analysis and demographic reporting. If the data were stratified by year, the first prescribing event of the calendar year used.

Descriptive summary statistics for the cohort outlined in Aim 1 were first investigated. This cohort represented all Medicaid recipients aged 18-64 prescribed a Gabapentinoid from 2009-2016. The cohort information was summarized for the entire study period and additionally stratified by year. Next, the overall number of gabapentinoid prescriptions and prescribing rates were examined, including the average number of Gabapentinoid prescriptions dispensed per patient by year. Additionally, descriptive statistics were conducted for average quantity dispensed per prescription, average length of supply, and GDD. Summary of analysis is shown in Table 3.6.

3.6.2 Aim 2

Aim 2 of this study was to determine rates and trends of a gabapentinoid co-prescribed with an opioid in South Carolina's Medicaid population. First,

Table 3.6 Analytical summary for Aim 1

Aim 1	Statistical Analysis	Objectives	Deliverables
To determine the prescribing patterns of gabapentinoids in South Carolina's Medicaid population.	Primary Outcome: Rates of gabapentinoid prescriptions filled at S.C. pharmacies between 2009-2016. Independent Variable: Gabapentinoid Rx Filled at S.C. Pharmacies Covariates: Recipient demographic characteristics listed in Table 1; Prescription characteristics (quantity, days supplied, refills), demographic information Analysis: Summary analysis	(1) To determine overall demographic information on South Carolina's Medicaid population which filled at least 1 gabapentinoid prescription from 2009-2016 (2) To determine rates of gabapentinoid prescriptions filled at S.C. pharmacies between 2009-2016. (3) To determine prescription characteristics of gabapentinoids	(A) Summary statistics of cohort population by year (mean age, % sex % race, etc.) presented in table format. (B) Summary statistics of all gabapentinoid prescriptions filled at S.C. pharmacies by Medicaid enrollees by year (2009-2016) presented in table format. To include: total gabapentinoid prescriptions by year (broken down by pregabalin and gabapentin), total number of patients who filled a gabapentinoid prescription by year, and average number of prescriptions filled per person. Data further stratified by age, sex, and race. (C) Average quantity, length of supply and daily dose stratified by year (broken down by pregabalin

		dispensed at SC pharmacies between 2009-2016.	and gabapentin) presented in table format.
		(4) To determine the percentage of prescriptions filled for gabapentinoids that exceed daily recommended doses.	(D) Percentage of prescriptions for gabapentin and pregabalin that exceed daily recommended doses presented in table format.

patients who filled at least 1 opioid prescription during the study period were identified to investigate the opioid prescribing variances of the population as a whole. Patients were then further investigated to determine if they had been prescribed an opioid and gabapentinoid concomitantly. All SC Medicaid recipients, aged 18-64 years who had at least 1 day of overlapped administration of a gabapentinoid and opioid prescription from 2009-2016 were included in the analysis. It is hypothesized that co-prescribing rates will be trending upwards in the state year over year.

Demographic and prescribing information were investigated to identify predictor variables that may explain gabapentinoid and opioid coadministration. An individual must have had at least one day of medication overlap to qualify as concomitant utilization. For the individual level analysis, the first prescribing event during the study period by patient was used for the statistical analysis. If the data was stratified by year, the first concomitant prescribing event of the calendar year was used. All prescriptions were identified by their unique NDC. Morphine equivalent daily dosages were calculated for all opioid prescriptions to compare potency.

Three main outcome measures are investigated for both gabapentin and pregabalin: (1) the rate of gabapentinoid and opioid concomitant utilization, (2) the daily dose of the co-prescribed gabapentinoid and opioid, and (3) the number of overlap days both medications were prescribed. Co-prescribing rates were

calculated over time (2009-2016). Similarly, to the analysis in Aim 1, a stratified analysis was conducted for patient demographic information. Summary of analysis is shown in Table 3.7.

3.6.3 Aim 3

Aim 3 of this study is to identify predictive factors associated with an increased likelihood of concomitant prescribing of a gabapentinoid and opioid in South Carolina's Medicaid population compared to a gabapentinoid prescription alone. It is hypothesized that these predictive factors will be similar to those found in opioid abuse including age, length of supply, and daily dosage (Joseph A. Boscarino, 2010; B. C. M. Mark J.Edlund, Ming-YuFan, AndreaDevries, Jennifer B.Braden and Mark D.Sullivan 2010; D. Mark J.Edlund, Teresa Hudson, Katherine M.Harris and MarkSullivan, 2007).

Diagnostic predictors were measured in the 12 months prior to the first prescribing event. These predictors were identified using ICD-9 and ICD-10 codes present in the first two diagnosis codes for either the primary or secondary diagnosis fields. FDA approved indications for gabapentin and pregabalin were identified in addition to previously identified predictors of opioid misuse and overdose. Diagnoses for fibromyalgia, diabetic peripheral nerve pain, seizures, restless leg syndrome, chronic pain, and mental health disorders were obtained

Table 3.7 Analytical summary for Aim 2

Aim 2	Statistical Analysis	Objectives	Deliverables
To determine rates and trends of the co-prescribing of a gabapentinoid with an opioid in South Carolina's Medicaid population.	Primary Outcome: Opioid Rx filled at S.C. pharmacies with a minimum of 1 overlap day with a gabapentinoid Rx between 2009-2016. Independent Variable: gabapentinoid and opioid Rx filled at S.C. pharmacies Covariates: Recipient demographic characteristics; prescription characteristics (type, dose, etc.) Analysis: Summary analysis (stratified by year)	(1) To determine overall demographic information for S.C. Medicaid population which has filled a gabapentinoid Rx concomitantly with an opioid Rx from 2009-2016. (2) To determine concomitant gabapentinoid and opioid prescription fill rates at S.C. pharmacies between 2009-2016. (3) To determine the prescription characteristics of gabapentinoid Rx's when	(A) Summary statistics of cohort population by year (mean age, % sex % race) presented in table format. (B) Summary statistics of all gabapentinoid Rx's (with concomitant opioid Rx's) filled at S.C. pharmacies by Medicaid enrollees by year (2009-2016) presented in table format. To include: total gabapentinoid prescriptions and patients with concomitant opioid prescribing by year (broken down by pregabalin and gabapentin). (C) Average quantity, length of supply and daily dose stratified by year (broken down by

		an opioid is co-administered. (4) To determine the percentage of prescriptions filled for gabapentinoids that exceed daily recommended doses when coprescribed with an opioid.	pregabalin and gabapentin) presented in table format. (D) Percentage of prescriptions for gabapentin and pregabalin (with concomitant opioid Rx) that exceed daily recommended doses presented in table format.

from patient office visits and hospital visits. A sensitivity analysis was conducted to include all diagnostic indicators from both HIC and HOSP files, however no statistical difference were observed.

Summary statistics for the cohort were first analyzed. Next, a bivariate analysis was first conducted to compare patients administered gabapentin only versus those who were co-administered a gabapentin and opioid. The dependent variable was concomitant utilization. The percentage of the total cohort was determined for each demographic and diagnostic characteristic. Bivariate analysis was conducted by Pearson's chi-squared test to asses for variances between dichotomous variables (sex, race, etc.). Paired students t-test was utilized to examine differences between means of continuous variables (ex. Daily Dosages, Days Prescribed, etc.). An alpha level of 0.05 was utilized to determine statistical significance. Finally a multiple logistic regression analysis which adjusted for demographic and diagnosis characteristics was then conducted. Figure 3.3 shows the proposed regression. Summary of analysis is shown in Table 3.8.

$$Log\ (Likelihood\ of\ Patient\ Coprescribed\ a\ Gabapentinoid\ and\ Opioid)$$
$$= \hat{\beta}_0 + \hat{\beta}_1 Age_i + \hat{\beta}_2 Gender_i + \hat{\beta}_3 Race_i + \hat{\beta}_4 QualCat_i$$
$$+ \hat{\beta}_5 PayCat_i + \hat{\beta}_7 Source_i + \hat{\beta}_8 Fibro_i + \hat{\beta}_9 DPN_i + \hat{\beta}_{10} Seizure$$
$$+ \hat{\beta}_{11} RLS_i + \hat{\beta}_{12} ChronicPain_i + \hat{\beta}_{13} MHD_i + \hat{\beta}_{14} OpioidAbuse_i$$
$$+ \hat{\beta}_{15} OpioidOD_i + \hat{\beta}_{16} TypeOfGaba_i + \hat{\beta}_{17} GabaExceed_i$$
$$+ \hat{\beta}_{18} LongTermGBNuse_i + \hat{\beta}_{19} LongTermPGNuse_i$$

Figure 3.3 Aim 3 Multivariate Regression Equation

Table 3.8 Analytical summary for Aim 3

Aim 3	Statistical Analysis	Objectives	Deliverables
To identify predictive factors associated with an increased likelihood of the prescribing and subsequent dispensing of a gabapentinoid and opioid concomitantly in South Carolina's Medicaid population.	Primary Outcome: Individuals of cohort will be converted to dichotomous variable. 0=Gabapentinoid Rx Only 1=Gabapentin Rx + Opioid Rx Covariates: Recipient demographic characteristics; prescription characteristics (type, dose, etc.) Analysis: Bivariate analysis, Multivariate logistic regression (logit)	(1) To determine significant differences between patients prescribed gabapentinoid only and those coprescribed a gabapentinoid and an opioid. (2) To determine odds ratios of increased likelihood that an individual will be co-prescribed an opioid and a gabapentinoid.	(A) A table listing the Chi-square bivariate analysis results including p values. (B) A table listing statistically significant predictive variables including odds ratios, confidence intervals (95%), and p values.

3.6.4 Aim 4

Aim 4 of this project is to determine if there is an association between ED visits for opioid overdose and the coprescribing of a gabapentinoid and opioid versus opioid prescribing alone. The occurrence of multiple ED visits is also investigated. It is hypothesized that a statistically significant increased occurrence of ED visits due to opioid overdose will be observed in patient coprescribed a gabapentinoid.

Diagnostics predictors were measured in the 12 months prior to the first prescribing event. A patient must then have been continuously enrolled a further 12 months after the prescribing event. Opioid overdose events were then measured following the first prescribing event. These diagnostic measures were identified using ICD-9 and ICD-10 codes present in the first two diagnosis codes for either the primary or secondary diagnosis field. FDA approved indications for gabapentin and pregabalin were identified in addition to previously reported predictors of opioid misuse and overdose. Diagnoses for fibromyalgia, diabetic peripheral nerve pain, seizures, restless less syndrome, chronic pain, and mental health disorders were obtained from patient office visits. Diagnoses for opioid abuse and opioid overdose were obtained from patient office visits and hospital visits.

Similar to Aim 3, the percentage of the total cohort was determined for each demographic and diagnostic characteristic. A bivariate analysis was first conducted to compare patients administered opioid prescriptions only versus those who were coadministered a gabapentinoid and an opioid. A multiple logistic analysis regression adjusted for demographic and diagnosis characteristics was then conducted. The dependent variable was opioid overdose. Figure 3.4 shows the proposed regression. Summary of analysis is shown in Table 3.9.

$$Log\ (Likelihood\ of\ Opioid\ Overdose) =$$

$$= \hat{\beta}_0 + \hat{\beta}_1 Age_i + \hat{\beta}_2 Gender_i + \hat{\beta}_3 Race_i + \hat{\beta}_4 QualCat_i$$

$$+ \hat{\beta}_5 PayCat_i + \hat{\beta}_7 Source_i + \hat{\beta}_8 Fibro_i + \hat{\beta}_9 DPN_i + \hat{\beta}_{10} Seizure$$

$$+ \hat{\beta}_{11} RLS_i + \hat{\beta}_{12} ChronicPain_i + \hat{\beta}_{13} MHD_i + \hat{\beta}_{14} OpioidAbuse_i$$

$$+ \hat{\beta}_{15} OpioidExceed_i$$

Figure 3.4 Aim 4 Multivariate Regression Equation

Table 3.9 Analytical summary for Aim 4

Aim 4	Statistical Analysis	Objectives	Deliverables
To determine if there is an association between emergency department visits for opioid overdose and the coprescribing of a gabapentinoid and opioid	Primary Outcome: ED visit for opioid overdose Covariates: Recipient demographic characteristics; prescription characteristics (type, dose, etc.) Analysis: Bivariate analysis, Multivariate logistic regression (logit)	(1) To determine significant differences between patients prescribed opioids only and those coprescribed a gabapentinoid and an opioid. (2) To determine odds ratios of increased likelihood that an individual will overdose if co-prescribed an opioid and a gabapentinoid versus a gabapentinoid only.	(A) A table listing the Chi-square bivariate analysis results including p values. (B) A table listing statistically significant predictive variables including odds ratios, confidence intervals (95%), and p values.

CHAPTER 4

Results

4.1 Aim 1 Results

Aim 1 focused on South Carolina Medicaid beneficiaries (aged 18-64) who received at least one gabapentinoid prescription throughout the study period, January 1, 2009 to December 31, 2016. Table 4.1 shows the summary statistics of this cohort including demographic characteristics. The first prescribing event of the study period was used for the analysis. For example, if a patient was prescribed a gabapentinoid every year of the study period, the first prescription from 2009 was utilized for age, source, type of gabapentinoid, etc. Over the study period, 50,773 South Carolina Medicaid beneficiaries received a gabapentinoid prescription. Recipients were primary female (71.9%), white (54.9%), and had an average age of 41.7 years. Approximately two thirds of recipients were enrolled in a health maintenance organization (HMO) as opposed to a fee-for-service (FFS) program. A total of nearly 500,000 gabapentinoid prescriptions were filled throughout the study period, with gabapentin prescriptions accounting for 84.6% of the overall total.

Table 4.1 Summary Statistics for Aim 1 Cohort: South Carolina Medicaid Recipients Prescribed a Gabapentinoid

Summary Statistics of Cohort (Medicaid Recipients of a Gabapentinoid, 2009-2016)	
Patient Characteristic	Number
Total Medicaid Recipients, 18-64	50,773
Age at first prescription (years), mean (SD)	41.7 (11.1)
Age at first prescription, n (%)	
18-29 years	8098 (16.4%)
30-39 years	14356 (29.1%)
40-49 years	13474 (27.3%)
50-64 years	14845 (29.2%)
Sex, n (%)	
Female	36516 (71.9%)
Male	14257 (28.1%)
Race, n (%)	
White	27850 (54.9%)
Black	14991 (29.5%)
Hispanic	545 (1.1%)
Other/Unknown	7387 (14.5%)
Qualifying Category, n (%)	
Disabled	29177 (57.6%)
AFDC	21167 (41.8%)
Other/Unknown	429 (0.8%)
Pay Category, n (%)	
Low Income families	22355 (44.1%)
SSI (Supplemental Security Income)	13066 (25.8%)
Aged, Blind, Disabled	6177 (12.2%)
Other/Unknown	7531 (14.8%)
Source, n (%)	
FFS	18024 (35.5%)
HMO	32749 (64.5%)
Total Gabapentinoid Rx Administered, n (%)	
Total Gabapentin Rx Administered	414940 (84.6%)
Total Pregabalin Rx Administered	75782 (15.4%)

Table 4.2 shows the summary statistics presented in Table 1 stratified by year. The first prescribing event per year was used for demographic information. For example, if a patient was prescribed a gabapentinoid in 2009, the first prescription from 2009 was utilized for age, type of gabapentinoid, dose etc. If this same patient was prescribed a gabapentinoid again in 2010, the demographic information from this year including age was utilized. Number of Medicaid beneficiaries prescribed a gabapentinoid increased from 7,610 in 2009 to 21,069 in 2016. In 2016 this accounted 6.8% of total adult beneficiaries, up from 3.7% in 2009. The average number of prescriptions filled per patient increased slightly from 4.4 in 2009 to 4.7 in 2016. Age increased from 41.8 to 45.2. The oldest age category (ages 50-64) showed the largest increases in overall percentage of the cohort from 27.8% in 2009 to 40.8% in 2016. The sex distribution remained consistent throughout the study period with approximately 73% female beneficiaries. The percentage of white beneficiaries dropped from 60.3% in 2009 to 51.3% in 2016; however this appears to be, at least in part, attributed to increased reporting of unknown/missing race. Of note is that recipients enrolled in an HMO program (rather than a FFS program) increased from 40.1% in 2009 to 86.2% in 2016. This increase in HMO enrollees corresponded to states efforts to expand managed care on a mandatory basis (SC Medicaid). Figure 4.1 shows the rising rate of gabapentinoid prescribing in South Carolina's Medicaid population.

Table 4.2 South Carolina Medicaid Recipients Prescribed a Gabapentinoid Stratified by Year, 2009-2016

Medicaid Beneficiaries Prescribed a Gabapentinoid (Pregabalin and Gabapentin) by Year								
	2009	2010	2011	2012	2013	2014	2015	2016
SC Medicaid Enrollees aged 18-64	205,000*	201,800*	190,000*	223,133	234,777	271,866	293,513	309,738
Beneficiaries Prescribed 1+ Gabapentinoids	7,610	9,063	10,326	11,652	12,947	16,173	18,444	21,069
Incidence Rate (Per 1,000 Enrollees)	37.1	44.9	54.3	52.2	55.1	59.5	62.8	68.0
% of Total Medicaid Enrollees Prescribed a Gabapentinoid	3.7%	4.5%	5.4%	5.2%	5.5%	5.9%	6.3%	6.8%
Avg # of Rx Dispensed Per Patient, mean (SD)	4.4 (4.1)	4.4 (4.1)	4.4 (4.0)	4.4 (4.0)	4.5 (4.0)	4.6 (4.0)	4.8 (4.1)	4.7 (3.9)
Age at first prescription (years), mean (SD)	41.8 (10.5)	41.8 (10.6)	42.2 (10.7)	42.8 (10.7)	43.6 (10.8)	43.8 (10.9)	44.4 (11.0)	45.2 (11.1)
18-29 years	1126 (14.8%)	1352 (14.9%)	1454 (14.1%)	1478 (12.67%)	1526 (11.8%)	1785 (11.0%)	1855 (10.1%)	1972 (9.4%)
30-39 years	2062 (27.1%)	2415 (26.7%)	2798 (27.1%)	3146 (27.0%)	3284 (25.4%)	4200 (26.0%)	4618 (25.0%)	5034 (23.9%)
40-49 years	2304 (30.3%)	2726 (30.1%)	2985 (28.9%)	3325 (28.5%)	3525 (27.2%)	4461 (27.6%)	4996 (27.1%)	5478 (26.0%)
50-64 years	2118 (27.8%)	2570 (28.4%)	3089 (29.9%)	3703 (31.8%)	4612 (35.6%)	5727 (35.4%)	6975 (37.8%)	8585 (40.8%)
Sex, n (%)								
Female	5633 (74.0%)	6632 (73.2%)	7520 (72.8%)	8507 (73.0%)	9423 (72.8%)	11752 (72.7%)	13422 (72.8%)	15159 (72.0%)

Male	1977 (26.0%)	2431 (26.8%)	2806 (27.2%)	3145 (27.0%)	3524 (27.2%)	4421 (27.3%)	5022 (27.2%)	5910 (28.1%)
Race, n (%)								
White	4591 (60.3%)	5381 (59.4%)	6084 (58.9%)	6806 (58.4%)	7319 (56.5%)	8879 (55.0%)	9749 (53.2)	10674 (51.3%)
Black	2153 (28.3%)	2586 (28.5%)	2929 (28.4%)	3333 (28.6%)	3778 (39.2%)	4708 (29.2%)	5474 (29.9)	6147 (29.6%)
Hispanic	50 (0.7%)	66 (0.7%)	85 (0.8%)	97 (0.8%)	113 (0.9%)	164 (1.0%)	171 (0.9%)	200 (1.0%)
Other/Unknown	816 (10.7%)	1030 (11.3%)	1228 (11.9%)	1416 (12.1%)	1737 (13.4%)	2399 (14.8%)	2938 (15.9%)	3769 (17.9%)
Qualifying Category, n (%)								
Disabled	4162 (54.7%)	4757 (52.5%)	5268 (51.1%)	5962 (51.2%)	6670 (51.6%)	7670 (47.5%)	8521 (46.3%)	9739 (46.25%)
AFDC	3375 (44.4%)	4233 (46.8%)	4973 (48.2%)	5594 (48.1%)	6167 (47.7%)	8355 (51.8%)	9747 (52.95%)	11171 (53.1%)
Other/Unknown	73 (1.0%)	73 (0.8%)	85 (0.8%)	96 (0.8%)	110 (0.9%)	148 (0.9%)	176 (1.0%)	159 (0.8%)
Pay Category, n (%)								
Low Income families	2883 (37.9%)	3640 (40.2%)	4227 (41.0%)	4751 (40.8%)	5183 (40.1%)	6926 (42.9%)	7818 (42.5%)	8445 (40.2%)
SSI (Supplemental Security Income)	3358 (44.2%)	3614 (39.9%)	3786 (36.7%)	4035 (34.7%)	4388 (34.0%)	4932 (30.6%)	5288 (28.7%)	5708 (27.2%)
Aged, Blind, Disabled	329 (4.3%)	608 (6.7%)	920 (8.9%)	1323 (11.3%)	1685 (13.0%)	2064 (12.8%)	2499 (13.6%)	3212 (15.3%)
Other/Unknown	1040 (13.6%)	1201 (13.2%)	1393 (13.5%)	1543 (13.3%)	1691 (13.1%)	2251 (13.9%)	2839 (15.5%)	3704 (17.6%)
Source, n (%)								

FFS	4552 (59.8%)	4766 (52.6%)	4689 (45.4%)	4558 (39.1%)	5157 (39.8%)	2371 (14.7%)	2592 (14.0%)	2895 (13.7%)
HMO	3058 (40.1%)	4297 (47.4%)	5637 (54.6%)	7097 (60.9%)	7790 (60.2%)	13802 (85.3%)	15852 (86.0%)	18174 (86.2%)

*Note: Age distributions were not available for years 2009-2011 and therefore an estimate using the % of adult enrollees from 2012 was utilized.

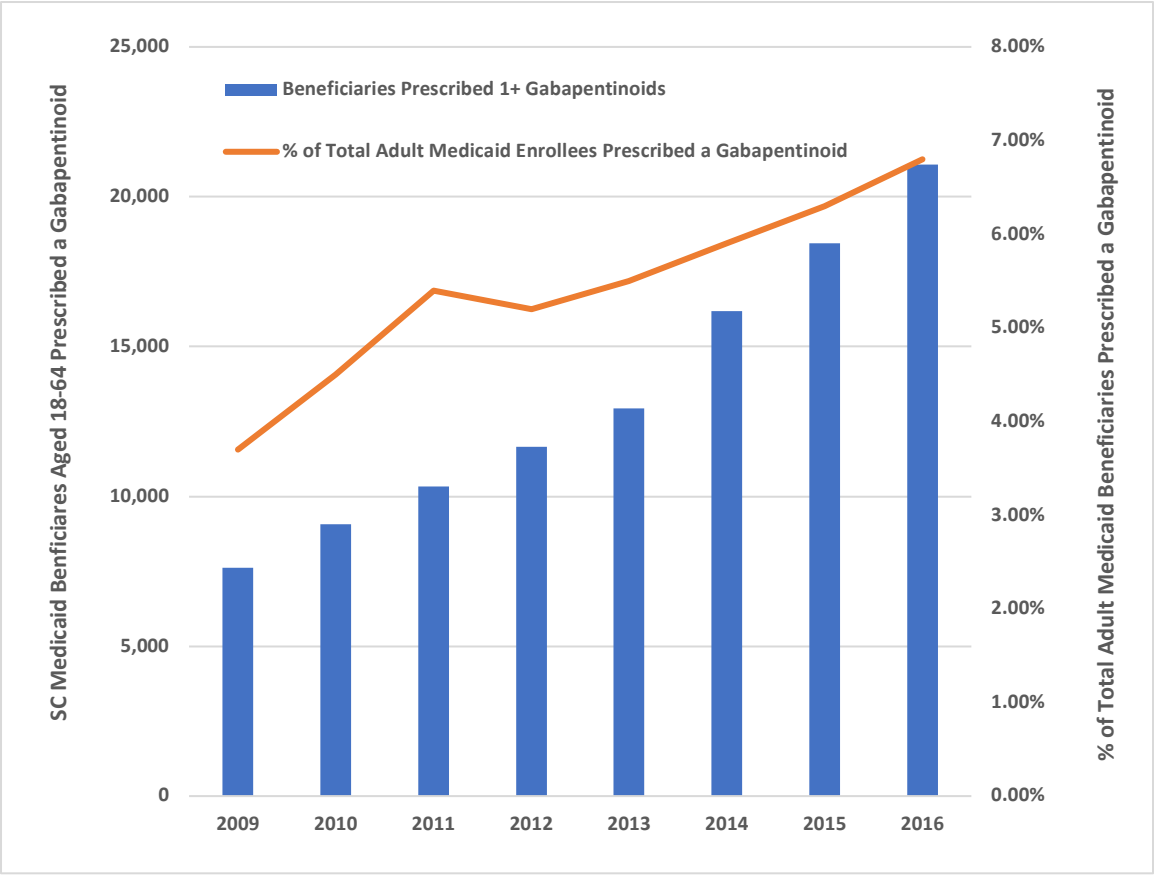

Figure 4.1 Gabapentinoid prescribing rates in South Carolina's Medicaid population by year, 2009-2016.

Table 4.3 shows detailed information on gabapentinoid prescriptions filled by year including average quantity dispensed per filled prescription, length of supply, total days prescribed per year, and daily dosages stratified for both gabapentin and pregabalin. Observations were excluded from the dosing statistical analysis if the quantity dispensed was >1000 due to the high probability that these were erroneous values. A sensitivity analysis was preformed using varying exclusion criteria for both quantity and average daily dosage which showed negligible differences in findings.

Table 4.3 Summary Statistics of Gabapentinoid Prescriptions dispended to Medicaid recipients, years 2009-2012

Gabapentinoid Prescriptions Dispensed by Year								
Gabapentin								
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Total # of Gabapentin Rx Dispensed	23204	30871	36498	43334	49020	65030	78331	88649
Quantity (Pill Count)[Ŧ] mean (std dev)	91 (47)	90 (46)	90 (44)	91 (43)	90 (41)	91 (42)	92 (42)	93 (41)
Length of Supply[Ŧ] mean (std dev)	30 (3.4)	29 (3.3)	30 (3.1)	30 (3.0)	30 (2.9)	30 (3.1)	30 (2.9)	30 (2.6)
Total Days Prescribed/Year[Ŧ] mean (std dev)	119(113)	119(112)	119(110)	127(12)	124(108)	128(111)	134(113)	132(109)
Dosage (mg/pill)[Ŧ] mean (std dev)	404(198)	404(198)	410(200)	413(200)	417(204)	422(206)	422(206)	431(206)
Daily Dosage (mg/day)[Ŧ] mean (std dev)	1289 (1251)	1255 (898)	1275 (985)	1291 (884)	1308 (1112)	1324 (881)	1337 (884)	1364 (872)
% of All Rx's where Avg Daily Dosage >1800mg[Ŧ]	16.8%	16.5%	16.7%	16.9%	17.4%	18.1%	18.9%	19.7%
Pregabalin								
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Total # of Pregabalin Rx Dispensed	10397	9323	8826	8437	9086	9488	10022	10206
Quantity (Pill Count)[Ŧ] mean (std dev)	67 (26)	70 (25)	70 (24)	69 (24)	66 (23)	67 (25)	67 (23)	68 (22)
Length of Supply[Ŧ] mean (std dev)	29 (5.3)	29 (3.4)	29 (3.8)	29 (4.6)	29 (6.2)	28 (6.2)	28 (5.7)	29 (5.3)
Total Days Prescribed/Year[Ŧ] mean (std dev)	122(115)	143(122)	149(126)	162(126)	140(112)	142(117)	150(119)	144(111)

Dosage (mg/pill)Ŧ mean (std dev)	119 (62)	126 (64)	130 (67)	137 (69)	143 (73)	142 (73)	140 (73)	142 (73)
Daily Dosage (mg/day)Ŧ mean (std dev)	277(226)	297(178)	306(218)	327(480)	327(170)	333(188)	331(324)	331(174)
% of All Rx's where Avg Daily Dosage >600mgŦ	1.0%	1.6%	1.7%	1.5%	0.7%	1.3%	0.8%	1.4%

Ŧ Missing values and quantity values >1000 excluded from statistical analysis

Total gabapentin prescriptions filled at South Carolina pharmacies for adult Medicaid recipients nearly quadrupled from 2009 to 2016 (23,204 filled prescriptions in 2009 to 88,649 filled prescriptions in 2016). The average pill quantity and length of supply for gabapentin prescriptions was generally consistent during the study period at approximately 90 pills and 30 days respectively. This is consistent with a 30-day supply and a 3 times/per day dosing regimen, common for gabapentin prescribing. The average total days per year a patient was prescribed gabapentin rose slightly from 119 days in 2009 to 132 days in 2016. The average daily dosage for gabapentin ranged from 1255 mg to 1364 mg throughout the study period. In 2009, 16.8% of prescriptions filled were above the maximum recommended daily maintenance dose (1800 mg/day) for postherpetic neuralgia; by 2016 this number had increased to 19.7%.

Conversely, total pregabalin prescriptions filled at South Carolina pharmacies for adults Medicaid recipients remained steady throughout the study period with 10,397 pregabalin prescriptions written in 2009 to 10,206 prescriptions in 2016. Similar to the gabapentin prescriptions, the average pill quantity and length of supply was largely constant during the study period at approximately 70 pills and 30 days respectively. This is approximately consistent with a 30-day supply of a 2 times/per day dosing regimen. The average total days per year a patient was prescribed pregabalin rose slightly from 122

in 2009 to 144 in 2016. The average recommended maximum daily dosage for pregabalin ranged from 277 mg to 331 mg throughout the study period. Pregabalin prescriptions filled that were above the recommended daily dose of 600 mg/day were less than 2% of total prescriptions throughout the study period. Figure 4.2 shows total gabapentinoid prescriptions filled at South Carolina pharmacies for adult Medicaid beneficiaries by year.

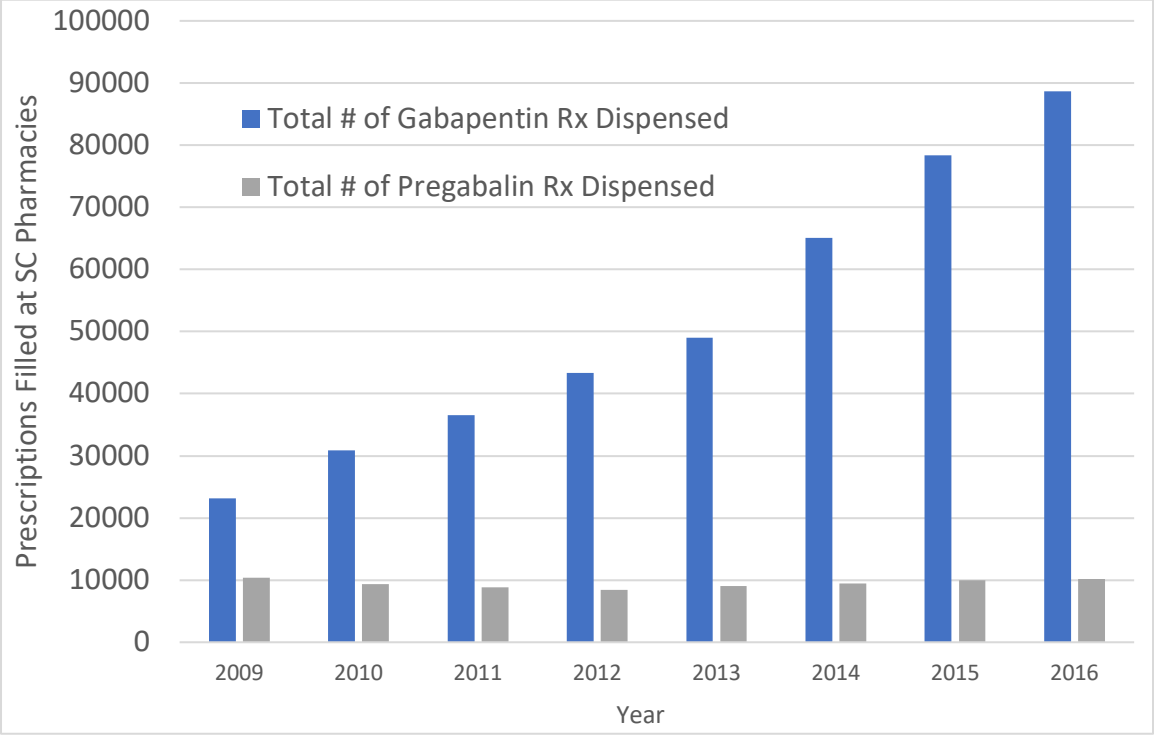

Figure 4.2 Total gabapentinoid prescriptions filled at South Carolina pharmacies for adult Medicaid beneficiaries by year, 2009-2016.

4.2 Aim 2 Results

Table 4.4 shows total opioid prescriptions dispensed to South Carolina Medicaid recipients, regardless of gabapentinoid coadministration. Over 300,000 opioid

Table 4.4 Summary Statistics of Opioid Prescriptions dispended to Medicaid recipients, years 2009-2012

Opioid Prescriptions Dispensed by Year								
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
SC Medicaid Enrollees aged 18-64	205,000*	201,800*	190,000*	223,133	234,777	271,866	293,513	309,738
Beneficiaries Prescribed 1+ Opioid	68,845	76,221	73,032	74,782	75,130	81,266	78,615	72,532
Incidence Rate (Per 1,000 Enrollees)	336	378	384	335	320	299	268	234
% of Total Medicaid Enrollees Prescribed An Opioid	33.6%	37.8%	38.4%	33.5%	32.0%	29.9%	26.8%	23.4%
Total # Opioid Rx Dispensed	301,426	342,696	322,597	338,248	336,129	382,765	356,792	315,404
Average Quantity (Pill Count)[Ŧ] mean (std dev)	54 (48)	56 (49)	63 (51)	65 (51)	65 (50)	65 (50)	66 (50)	69 (50)
Average Length of Supply [Ŧ] mean (std dev)	13.6 (14.3)	14.3 (11.6)	16.3 (11.7)	16.9 (11.8)	17.1 (11.8)	17.4 (11.9)	17.9 (12.0)	18.9 (11.9)
Average MEDD (mg/day)[Ŧ] mean (std dev)	53 (63)	50 (61)	47 (56)	47 (53)	45 (48)	44 (48)	45 (48)	46 (47)
% of Rx where MEDD >120mg	7.0%	5.9%	4.6%	4.7%	4.3%	4.1%	4.4%	4.6%

prescriptions were dispensed each year, peaking in 2014 with 382,765 prescriptions dispensed to 81,266 recipients. Average pill quantity dispensed per prescription increased from 54 pills in 2009 to 69 pills in 2016. Average length of supply also increased throughout the study period from 13.4 days to 18.9 days per prescription. Conversely, the Morphine Equivalent Daily Dosage (MEDD), a normalized measure of opioid potency, decreased over time from 53 in 2009 to 43 in 2016. Additionally, the percentage of opioid prescriptions that exceeded a MEDD of 120, often considered to be a dosage that carries higher risk for adverse drug events, decreased from 7.0% in 2009 to 4.6% in 2016.

Table 4.5 shows detailed prescribing information for gabapentinoid and opioid prescriptions which were administered concomitantly. For patients administered a prescription for a gabapentinoid, coadministration of an opioid was extremely common. Nearly 70% of all patients who were prescribed a gabapentinoid in 2009 were also administered an opioid for at least one day of overlap. This percentage decreased to approximately 60% by 2016. Average days of overlap per calendar year increased from 72 days in 2009 to 82 days in 2016. The average number of opioid prescriptions written per year to patients coadministered a gabapentinoid and an opioid decreased over the study period from 10.1 to 7.7, as did the MEDD and the percent of prescriptions in which the MEDD was >120 mg/day. Conversely the average pill quantity dispensed and the average length of supply increased.

Table 4.5 Summary Statistics of Opioid Prescriptions Dispended to Medicaid Recipients, years 2009-2012

Concomitant Administration of an Opioid and Gabapentinoid Rx by Year								
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Total Patients Prescribed a Gabapentinoid, n	**7,610**	**9,063**	**10,326**	**11,652**	**12,947**	**16,173**	**18,444**	**21,069**
Total Patients Prescribed a Gabapentinoid+Opioid Concomitantly (1 or more days of overlap), n	5,317	6,439	6,991	7,902	8,773	11,082	11,923	12,608
% Of Patients with Concomitant Opioid and Gabapentin Administration	69.9%	71.0%	67.7%	67.8%	67.8%	68.5%	64.6%	59.8%
Average Days of Overlap, mean (std dev)	73 (86)	75 (87)	78 (88)	79 (88)	80 (88)	83 (90)	86 (94)	84 (91)
Average Number of Opioid Rx Dispended During Year, mean (std dev)	10.1 (7.5)	9.9 (7.2)	9.3 (6.6)	9.3 (6.6)	8.9 (6.3)	9.1 (6.4)	8.5 (6.3)	7.7 (5.6)
Average Number of Gabapentinoid Rx During Year, mean (std dev)	4.9 (4.2)	4.8 (4.2)	4.9 (4.1)	4.9 (4.1)	5.0 (4.1)	5.2 (4.1)	5.5 (4.2)	5.5 (4.0)
Opioids								
	2009	2010	2011	2012	2013	2014	2015	2016
Total Number of Opioid Rx Dispensed, n	53,759	63,699	64,699	73,194	77,843	100,644	101,765	97,076
Average Quantity (Pill Count)[Ŧ] mean (std dev)	71 (52)	74 (58)	80 (56)	80 (52)	80 (50)	71 (52)	78 (49)	80 (48)
Average Length of Supply[Ŧ] mean (std dev)	18.9 (11.3)	19.6 (11.2)	21.2 (10.7)	21.5 (10.6)	21.9 (10.5)	21.7 (10.7)	22.1 (10.7)	22.8 (10.3)
Average Daily Dosage (MEDD)[Ŧ] mean (std dev)	57 (69)	53 (64)	51 (61)	51 (57)	49 (52)	47 (52)	48 (49)	49 (49)
% of Rx where Avg Daily Dosage >120MEDD[Ŧ]	8.0%	7.0%	6.7%	6.8%	5.9%	5.2%	5.3%	5.5%

Gabapentinoids								
Total Number Gabapentinoid Rx Dispensed, n	25,821	31,197	33,911	38,796	43,687	58,472	65,615	69,143
Total Number Gabapentin, n	17,289	23,447	26,813	32,153	36,290	49,345	57,366	61,047
% of Total Gabapentinoids	67.0%	75.2%	79.1%	82.9%	83.1%	84.4%	87.4%	88.3%
Average Quantity (Pill Count)Ŧ, mean (std dev)	93 (45)	91 (42)	91 (41)	92 (41)	93 (42)	93 (40)	95 (43)	95 (40)
Average Total Days Prescribed Per YearŦ, mean (std dev)	226 (122)	229 (129)	226 (125)	214 (122)	224 (138)	231 (119)	239 (124)	234 (118)
Average Length of SupplyŦ mean (std dev)	29.5 (3.3)	29.5 (3.2)	29.5 (3.1)	29.6 (2.8)	29.6 (2.8)	29.5 (3.0)	29.5 (2.8)	29.6 (2.5)
Average Daily Dosage (mg/day)Ŧ mean (std dev)	1365 (29)	1311 (901)	1349 (989)	1366 (905)	1390 (1010)	405 (898)	1420 (904)	1454 (866)
% of Rx where Avg Daily Dosage >1800mgŦ	19.0%	18.0%	18.5%	19.1%	20.0%	20.5%	21.4%	22.7%
% of Rx where Avg Daily Dosage >3600mgŦ	1.1%	0.7%	0.6%	0.7%	0.4%	0.3%	0.6%	0.4%
Total Number Pregabalin, n	8,532	7,750	7,098	6,643	7,397	7,869	8,249	8,096
% of Total Gabapentinoids	33.0%	24.8%	20.9%	17.1%	16.9%	13.5%	12.6%	11.7%
Average Quantity (Pill Count)Ŧ mean (std dev)	68 (26)	71 (25)	70 (24)	70 (24)	66 (21)	68 (25)	68 (23)	68 (22)
Average Length of SupplyŦ mean (std dev)	28.7 (5.2)	29.5 (3.2)	29.4 (3.8)	29.2 (4.6)	28.5 (5.5)	28.2 (6.2)	28.4 (5.6)	28.6 (5.2)
Average Total Days Prescribed Per Year)Ŧ, mean (std dev)	232 (133)	252 (135)	260 (142)	222 (109)	220 (106)	240 (121)	245 (116)	231 (100)
Average Daily Dosage (mg/day)Ŧ mean (std dev)	286 (251)	305 (182)	315 (228)	331 (177)	327 (170)	337 (189)	339 (347)	336 (173)
% of Rx where Avg Daily Dosage >600mgŦ	1.1%	1.9%	1.7%	1.6%	0.7%	1.2%	0.8%	1.3%

Interestingly, pregabalin accounted for 33.0% of all concomitant gabapentinoid prescriptions in 2009, but dropped to just over 10% by 2016. The average number of gabapentinoid prescriptions written per calendar year increased slightly over the study period from 4.9 prescriptions to 5.4 prescriptions. Average pill quantity dispensed and average length of supply remained consistent throughout the study period for both pregabalin and gabapentin. Conversely, average daily dosage increased for both. Average gabapentin prescription daily dosage increased from 1365 mg in 2009 to 1454 mg in 2016. The average prescription daily dosage for pregabalin increased from 286 mg in 2009 to 336 mg in 2016. The percentage of prescriptions which exceeded recommended daily maintenance dosages for postherpetic neuralgia increased slightly for gabapentin from 19.0% in 2009 to 22.7% in 2016. Doses that exceeded daily dose recommendations for pregabalin remained relatively unchanged at less than 2% throughout the study period. Total days per year prescribed a gabapentinoid was above 200 days throughout the entire study period.

4.3 Aim 3 Results

Table 4.6 shows summary statistics for the Aim 3 cohort. The cohort consisted of South Carolina Medicaid enrollees aged 18-64 prescribed a gabapentinoid between 2009-2016 who were continuously enrolled during the 12 months prior to their first prescribing event and did not have a history of a cancer pain diagnosis. 16,475 patients met eligibility requirements for inclusion in Aim 3, representing approximately one third of beneficiaries identified in Aim 1. The

Table 4.6 Summary Statistics for Aim 3 Cohort: South Carolina Medicaid Recipients Prescribed a Gabapentinoid, years 2009-2012 with 12 months of Continual Enrollment Prior to First Prescribing Event

Summary Statistics of Aim 3 Cohort	
Characteristics	Number (%)
Demographics	
Total Cohort	16475 (100%)
Age at first overlap prescription	
18-29 years	1925 (11.7%)
30-39 years	4173 (25.3%)
40-49 years	4924 (29.9%)
50-64 years	5453 (33.1%)
Sex	
Female	12218 (74.2%)
Male	4257 (25.8%)
Race	
White	8764 (53.2%)
Black	5611 (34.1%)
Hispanic	146 (0.9%)
Other/Unknown	2954 (11.9%)
Medicaid Information	
Qualifying Category	
Disabled	7739 (47.0%)
AFDC	8623 (52.3%)
Other/Unknown	113 (0.7%)
Pay Category	
Low Income families	7673 (46.6%)
SSI (Supplemental Security Income)	7723(46.9%)
Aged, Blind, Disabled	397 (2.4%)
Other/Unknown	682 (4.1%)
Source, n (%)	
FFS	13097 (79.5%)
HMO	3378 (20.5%)
Diagnosis Predictors	
Fibromyalgia	1673 (10.2%)
Diabetic Peripheral Nerve Pain (DPN)	499 (3.0%)
Seizures	516 (3.1%)
Restless Leg Syndrome	184 (1.1%)
Chronic Pain	1995 (12.1%)
Mental Health Disorders	6657 (40.1%)
Opioid Abuse	429 (2.6%)
Opioid Overdose	45 (0.3%)

Gabapentin Prescribing	
Type of Gabapentinoid	
Gabapentin	14905 (90.5%)
Pregabalin	1570 (9.5%)
Gabapentinoid Dosing Exceeds Recommendations	795 (4.8%)
Long term Gabapentin use (>180 days)	2736 (16.6%)
Long term Pregabalin use (>180 days)	420 (2.6%)

cohort was predominately female (74.2%) and white (53.2%). Patients were primarily over 30 years of age, with only 11.7% in the 18-29 years age category. Approximately 80% of beneficiaries were enrolled in a fee-for-service program. Nearly equal numbers of enrollees were classified in the low-income family (46.6%) and supplemental security income (46.9%) payment categories.

Additionally, over 90% of the gabapentinoid prescriptions filled by the cohort were for gabapentin. Of the approved indications for gabapentinoids, fibromyalgia was identified most frequently (10.2%). However, it is important to note that pregabalin is the only gabapentinoid currently approved for the treatment of fibromyalgia. Diabetic peripheral nerve pain, history of seizures, and restless leg syndrome were all indicated in 3.1% or less of patients. A history of a mental health disorder was the most frequently identified of all diagnostic predictors at 40.1% of the cohort. 2.6% of patients had a history of opioid abuse and 0.3% had experienced an opioid overdose event in the last 12 months. Chronic pain was indicated in 12.1% of the cohort. Gabapentinoid prescriptions that exceeded daily maintenance dosage recommendations were administered to 4.8% of all patients.

Table 4.7 is a summary of the chi-squared and t-test analyses. Nearly 70% of the cohort had at least one day of gabapentin and opioid prescription overlap. White beneficiaries were much more likely to be prescribed a gabapentinoid and opioid concomitantly (57.1% vs 44.5%; p <0.0001). Conversely black beneficiaries were significantly less likely to be concomitantly administered both medications (43.2% vs 30.2%; p<0.0001). Sex was not significantly different between groups (p=0.2056).

Table 4.7 Bivariate analysis comparison of SC Medicaid Recipients Prescribed Gabapentin With and Without a Concomitant Opioid Prescription, 2009-2016

Bivariate Analysis Aim 3			
Characteristics	GABA Only	GABA + Opioid	p value
Demographics			
Total Cohort	4999	11476	-
Age at first overlap prescription, n (%)			
18-29 years	751 (15.1%)	1174 (10.2%)	<0.0001
30-39 years	1270 (25.5%)	2903 (25.3%)	
40-49 years	1405 (28.2%)	3519 (30.7%)	
50-64 years	1573 (31.6%)	3880 (33.9%)	
Sex, n (%)			
Female	3740 (75.2%)	8478 (74.0%)	0.2056
Male	1259 (25.3%)	2998 (26.2%)	
Race, n (%)			
White	2214 (44.5%)	6550 (57.1%)	<0.0001
Black	2151 (43.2%)	3460 (30.2%)	
Hispanic	66 (1.3%)	80 (0.7%)	
Other/Unknown	568 (11.4%)	1386 (12.1%)	
Medicaid Information			
Qualifying Category, n (%)			
Disabled	2676 (53.8%)	5063 (44.1%)	<0.0001
AFDC	2282 (45.9%)	6341 (55.3%)	
Other/Unknown	41 (0.8%)	72 (0.6%)	
Pay Category, n (%)			
Low Income Families	2537 (51.0%)	5136 (44.8%)	<0.0001

SSI (Supplemental Security Income)	2051 (41.2%)	5672(49.5%)	
Aged, Blind, Disabled	129 (2.6%)	268 (2.3%)	
Other/Unknown	282 (5.7%)	400 (3.5%)	
Source, n (%)			
FFS	672 (13.5%)	2706 (23.6%)	<0.0001
HMO	4327 (87.0%)	8770 (76.5%)	
Diagnosis Predictors			
Fibromyalgia	304 (6.1%)	1369 (11.9%)	<0.0001
Diabetic Peripheral Nerve Pain (DPN)	117 (2.4%)	382 (3.3%)	0.0008
Seizures	158 (3.2%)	358 (3.1%)	0.8609
Restless Leg Syndrome	51 (1.0%)	133 (1.2%)	0.4483
Chronic Pain	269 (5.4%)	1726 (15.1%)	<0.0001
Mental Health Disorders	1875 (37.7%)	4782 (41.7%)	<0.0001
Opioid Abuse	126 (2.5%)	303 (2.6%)	0.6571
Opioid Overdose	12 (.2%)	33 (.3%)	0.5912
Gabapentin Prescribing			
Gabapentin, n (%)	4712 (94.7%)	10193 (88.9%)	<0.0001
Daily Dosage mean (std dev)	698 (465)	984 (727)	<0.0001
Total Days Per Year Prescribed mean (std dev)	63 (61)	109 (97)	<0.0001
Long-term use (>180 days) n (%)	342 (6.9%)	2394 (22.9%)	<0.0001
Pregabalin, n (%)	287 (5.8%)	1283 (11.2%)	<0.0001
Pregabalin Daily Dosage mean (std dev)	175 (102)	239 (145)	<0.0001
Total Days Per Year Prescribed, mean (std dev)	60 (60)	116 (103)	<0.0001
Long term use (>180 days) n (%)	19 (5.8%)	401 (26.4%)	<0.0001
Gabapentinoid Dosing Exceeds Recommendations, n (%)	75 (1.5%)	720 (6.3%)	<0.0001

Diagnostic predictors which were associated with a significant increase in concomitant opioid and gabapentin utilization included fibromyalgia (11.9% vs 6.1%; p<0.001), diabetic peripheral nerve pain (3.3% vs 2.4%, p=0.0008), chronic pain (15.1% vs 5.4% p =<0.0001), and mental health disorder (41.7% vs

37.7% p<0.0001). Indications for seizures, restless leg syndrome, opioid abuse, and opioid overdose were not statistically different between groups. Figure 4.3 shows a graphical representation of the bivariate analysis for diagnostics predictors.

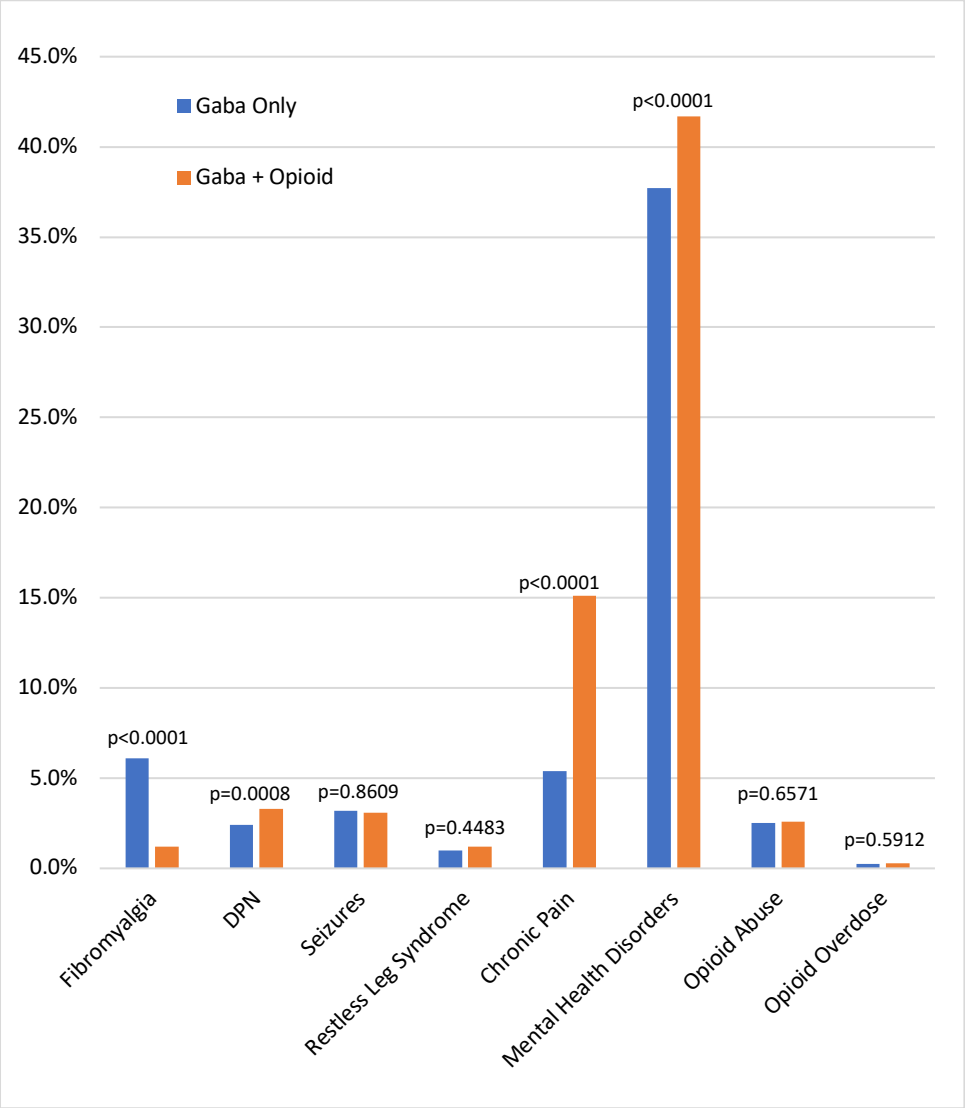

Figure 4.3 Comparison of SC Medicaid Recipients Prescribed Gabapentin With and Without a Concomitant Opioid Prescription, 2009-2016: Graphical representation of the bivariate analysis for diagnostic predictors

Of the gabapentinoids, a prescription for pregabalin was significantly more likely to be prescribed concomitantly with an opioid (11.2% vs 5.8%; $p<0.0001$). Daily dosages and total days per year prescribed a gabapentinoid were both significantly larger when coprescribed with a gabapentinoid for both gabapentin and pregabalin.

Table 4.8 shows the results for the multivariate logistical regression analysis, including adjusted and unadjusted (crude) odd ratios. For the adjusted odd ratios, an increased likelihood for the coadministration of a gabapentin and opioid occurred for all age groups when referenced to 18-29 year old's. Black (OR = 0.573; 95% CI: 0.529 – 0.621) and Hispanic (OR = 0.466; 95% CI: 0.329 – 0.660) patients were significantly less likely to utilize a gabapentinoid and opioid concomitantly compared to white beneficiaries. Gender was not a significant predictor of coadministration in the model. Patients enrolled in a FSS plan compared to an HMO plan were less likely to have concomitant utilization (OR= 0.564; 95% CI: 0.510 – 0.625).

Notable diagnostic predictors which were associated with an increased likelihood of concomitant utilization included fibromyalgia (OR = 1.831; 95% CI: 1.599 – 2.097), diabetic peripheral nerve pain (OR = 1.388; 95% CI: 1.111 - 1.735), and chronic pain (OR = 3.151; 95% CI: 2.746 - 3.616). Patients prescribed pregabalin rather than gabapentin were also at an increased likelihood of co-administration (OR = 1.367; 95% CI: 1.175 – 1.592). In addition, a gabapentinoid prescription that exceed recommended maintenance dosing increased the odds of

Table 4.8. Logistic Regression of Gabapentin and Opioid Concomitant Prescriptions, Adjusting for Demographic and Diagnostic Predictors, years 2009-2012

Characteristics	Adjusted OR (95% CI)	Model Coefficient p value	Unadjusted OR (95% CI)	Model Statistic p value
Demographics				
Age				
18-29	1 [Reference]			
30-39	1.330 (1.178 - 1.501)	<0.0001	1.462 (1.306 – 1.637)	<0.0001
40-49	1.341 (1.189 - 1.511)	<0.0001	1.602 (1.435 – 1.790)	<0.0001
50-64	1.241 (1.093 - 1.409)	0.0008	1.578 (1.415 – 1.759)	<0.0001
Male	0.946 (0.870 - 1.029)	0.1951	1.050 (0.973 -1.133)	0.2077
Race/ethnicity				
White	1 [Reference]			
Black	0.573 (0.529 -0.621)	<0.0001	0.544 (0.506 – 0.584)	<0.0001
Hispanic	0.466 (0.329 -0.660)	<0.0001	0.410 (0.295 – 0.570)	<0.0001
Other	0.732 (0.650 - 0.842)	<0.0001	0.825 (0.740 – 0.920)	<0.0001
Medicaid Information				
Qualifying Category				
AFDC	1 [Reference]			
Disabled	1.793 (1.467 - 2.191)	0.0001	1.469 (1.374 – 1.570)	<0.0001
Other/Unknown	1.275 (0.825 - 1.971)	0.2744	0.928 (0.613 – 1.366)	0.7052
Pay Category				
Low Income families	1 [Reference]			
SSI (Supplemental Security Income)	0.721 (0.589 - 0.883)	0.0016	1.366 (1.274 – 1.464)	<0.001
Aged, Blind, Disabled	0.516 (0.384 - 0.693)	<0.0001	1.026 (0.827 – 1.273)	0.8138

Other/Unknown	0.537 (0.445 - 0.649)	<0.0001	0.701 (0.597 – 0.822)	<0.001
Source				
FFS	0.564 (0.510 - 0.625)	<0.0001	0.503 (0.459 – 0.552)	<0.001
Diagnostic Predictors				
Fibromyalgia	1.831 (1.599 - 2.097)	<0.0001	2.085 (1.832 – 2.372)	<0.0001
Diabetic Peripheral Nerve Pain (DPN)	1.388 (1.111 – 1.735)	0.0040	1.432 (1.161 – 1.766)	0.0008
Seizures	0.810 (0.661 - 0.993)	0.0430	0.983 (0.813 – 1.189)	0.8605
Restless Leg Syndrome	1.037 (0.736 -1.460)	0.8362	1.134 (0.820 – 1.568)	0.4486
Chronic Pain	3.151 (2.746 - 3.616)	<0.0001	3.102 (2.715 – 3.543)	<0.0001
Mental Health Disorders	0.975 (0.904 - 1.052)	0.5165	1.184 (1.106 – 1.268)	<0.0001
Opioid Abuse	0.843 (0.673 - 1.057)	0.1391	1.048 (0.849 – 1.294)	0.6600
Opioid Overdose	0.884 (0.434 - 1.800)	0.7340	1.198 (0.617 – 2.322)	0.5917
Gabapentin Prescribing				
Type of Gabapentinoid (Ref Gabapentin)	1.367 (1.175 - 1.592)	<0.0001	2.067 (1.810 – 2.359)	<0.0001
Gabapentinoid Dosing Exceeds Recommendations	3.088 (2.398 - 3.975)	<0.0001	4.395 (3.456 – 5.588)	<0.0001
Long term Gabapentin use (>180 days)	3.336 (2.949 - 3.774)	<0.0001	3.589 (3.187 – 4.041)	<0.0001
Long term Pregabalin use (>180 days)	6.555 (3.962-10.875)	<0.0001	9.483 (5.979 -15.041)	<0.0001

concomitant utilization by 3.068 (95% CI: 2.398 – 3.975). Conversely, individuals with a history of seizures were at decreased likelihood of co-prescribing (OR = 0.810; 95% CI: 0.661 – 0.993). Restless leg syndrome, opioid abuse, opioid overdose, and mental health disorders were not predictors of concomitant utilization in the model.

4.4 Aim 4 Results

Table 4.9 shows summary statistics for the Aim 4 cohort. The cohort consisted of South Carolina Medicaid enrollees aged 18-64 years prescribed an opioid between 2009-2016 who were continuously enrolled during the 12 months prior to and following their first prescribing event and did not have a history of a cancer pain diagnosis. 34,497 patients met eligibility requirements for inclusion in Aim 4, representing approximately one half of beneficiaries identified in Aim 2. Of the identified cohort, 34,497 patients were prescribed an opioid only and 10,278 were prescribed an opioid and gabapentinoid concomitantly.

Table 4.9 Summary Statistics for Aim 4 Cohort: South Carolina Medicaid Recipients Prescribed a Gabapentinoid, years 2009-2012 with 12 months of Continual Medicaid Enrollment Prior to and Following First Prescribing Event

Summary Statistics of Aim 4 Cohort	
Characteristics	Number (%)
Demographics	
Total Cohort	45183 (100%)
Opioid Overdose	557 (1.2%)
Opioid Only Patients	34497 (76.2%)
Concomitant Gaba and Opioid Patients	10278 (22.8%)
Age at first overlap prescription	
18-29 years	10227 (22.6%)

30-39 years	11103 (24.6%)
40-49 years	11782 (26.1%)
50-64 years	12071 (26.7%)
Sex	
Female	32357 (71.6%)
Male	12826 (28.4%)
Race	
White	20820 (46.1%)
Black	18504 (41.0%)
Hispanic	382 (0.8%)
Other/Unknown	5577 (12.1%)
Medicaid Information	
Qualifying Category	
Disabled	17874 (39.3%)
AFDC	27051 (59.5%)
Other/Unknown	566 (1.24%)
Pay Category	
Low Income families	17849 (39.5%)
SSI (Supplemental Security Income)	25136 (55.6%)
Aged, Blind, Disabled	618 (1.4%)
Other/Unknown	2228 (4.9%)
Source	
FFS	19195 (42.5%)
HMO	25988 (57.5%)
Diagnosis Predictors	
Fibromyalgia	10786 (23.9%)
Diabetic Peripheral Nerve Pain (DPN)	3383 (7.5%)
Seizures	4374 (9.7%)
Restless Leg Syndrome	1160 (2.6%)
Chronic Pain	14201 (31.4%)
Mental Health Disorders	28090 (62.2%)
Opioid Abuse	3011 (6.7%)
Opioid Prescribing	
Opioid Prescription Exceed 120 MEDD	2278 (5.0%)

The cohort was predominantly female (71.6%) and primarily white (46.1%) and black (41.0%). Age was generally distributed equally between the four age groups. The cohort largely qualified for Medicaid through aid for families with

dependent children (59.5%), were reported under the supplemental security income pay category (55.8%), and were enrolled in an HMO at the time of the first prescribing event (57.5%). Chronic pain (31.4%), mental health disorders (62.2%), and fibromyalgia (23.9%) were the three most common diagnostic indications in the cohort. Diabetic peripheral nerve pain, history of seizures, and restless leg syndrome were all indicated in 10% or less of patients. Approximately 5% of patients filled a prescription which exceeded 120 morphine equivalent daily dosage and 6.7% of patients had a history of opioid abuse.

Table 4.10 is a summary of the bivariate analysis. An overdose diagnosis was indicated in 557 (1.3%) patients in the cohort. Sex was the only demographic indicator that was not significantly different between groups (p=0.9914). Age, qualifying category, pay category, and source were all statistically different. White beneficiaries were much more likely to experience an overdose (OD=72.2% vs No OD=45.8%; p <0.0001) than black beneficiaries (OD=15.1% vs No OD=41.3%; p<0.0001). The age group of 40-49 year old's were the most likely to experience an overdose event (OD=35.9% vs No OD=26.0% p<0.001).

Diagnostic predictors which had higher prevalence in the overdose group included fibromyalgia (OD=46.1% vs No OD=23.6%; p<0.001), diabetic peripheral nerve pain (OD=11.1% vs No OD=7.4%; p=0.0010), seizures (OD=25.0% vs No OD=9.5%; p<0.0001), restless leg syndrome (OD=4.7% vs No OD=2.5%; p=0.016), chronic pain (OD=73.3% vs No OD=30.9%; p<0.0001), mental health disorders (OD=91.7% vs No OD=61.8%; p<0.0001), and opioid

Table 4.10 Comparison of SC Medicaid Recipients Prescribed an Opioid With and Without an indication of Opioid Overdose, 2009-2016

Aim 4 Bivariate Analysis			
Characteristics	**No OD**	**OD**	**p value**
Demographics			
Total Cohort	44,626	557	-
Concomitant Gabapentinoid Prescribing	10,055 (22.5%)	223 (40.0%)	<0.0001
Age at first overlap prescription, n (%)			<0.0001
18-29 years	10,155 (22.8%)	72 (12.9%)	
30-39 years	10,977 (24.6%)	126 (22.6%)	
40-49 years	11,582 (26.0%)	200 (35.9%)	
50-64 years	11,912 (26.7%)	159 (28.5%)	
Sex, n (%)			0.9914
Female	31,958 (71.6%)	399 (71.6%)	
Male	12,668 (28.4%)	158 (28.4%)	
Race, n (%)			<0.0001
White	20,418 (45.8%)	402 (72.2%)	
Black	18,420 (41.3%)	84 (15.1%)	
Hispanic	381 (0.9%)	1 (0.2%)	
Other/Unknown	5,407 (12.1%)	70 (12.6%)	
Medicaid Information			
Qualifying Category, n (%)			<0.0001
Disabled	17,731 (39.7%)	118 (21.2%)	
AFDC	26,335 (59.0%)	434 (77.9%)	
Other/Unknown	560 (1.3%)	5 (0.9%)	
Pay Category, n (%)			<0.0001
Low Income Families	17,082 (38.3%)	119 (21.4%)	

SSI (Supplemental Security Income)	24,718 (55.4%)	418 (75.0%)	
Aged, Blind, Disabled	607 (1.4%)	11 (2.0%)	
Other/Unknown	2219 (5.0%)	9 (1.6%)	
Source, n (%)			
FFS	18,922 (42.4%)	273 (49.0%)	0.0017
HMO	25,704 (57.6%)	284 (51.0%)	
Diagnosis Predictors			
Fibromyalgia	10,529 (23.6%)	257 (46.1%)	<0.0001
Diabetic Peripheral Nerve Pain (DPN)	3321 (7.44%)	62 (11.1%)	0.0010
Seizures	4,235 (9.5%)	130 (25.0%)	<0.0001
Restless Leg Syndrome	1134 (2.5%)	26 (4.7%)	0.0016
Chronic Pain	13,793 (30.9%)	408 (73.3%)	<0.0001
Mental Health Disorders	27,579 (61.8%)	511 (91.7%)	<0.0001
Opioid Abuse	2767 (6.2%)	244 (43.8%)	<0.0001
Opioid Prescribing			
Opioid Prescription Exceed 120 MEDD	2221 (5.0%)	57 (10.2%)	<0.0001

abuse (OD=43.8% vs No OD=6.2%; p<0.0001). Figure 4.4 shows a graphical representation of the bivariate analysis for diagnostics predictors. Opioid prescriptions exceeding a daily MEDD of 120 or above were also associated at increased likelihood of overdose (OD=10.2% vs No OD =5.0%; p<0.001).

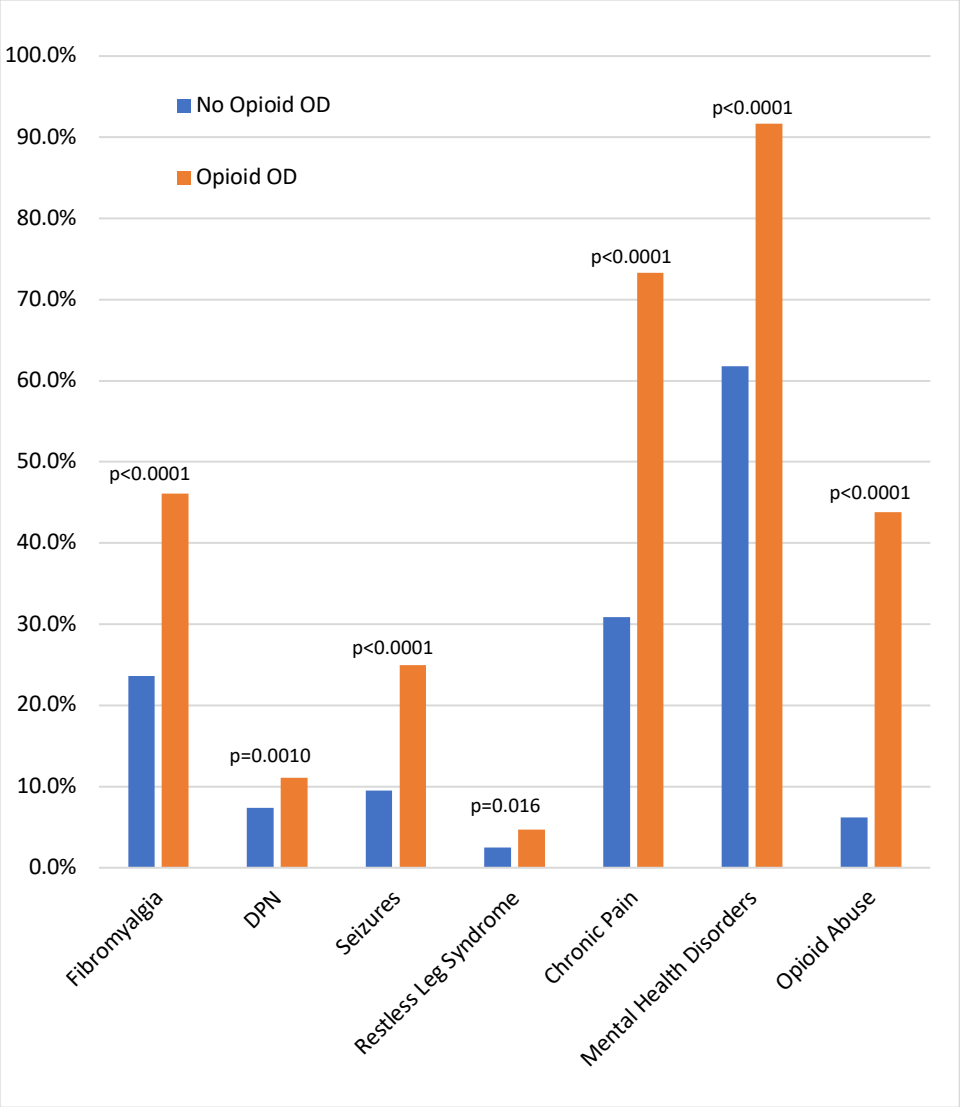

Figure 4.4 Comparison of SC Medicaid Recipients Prescribed an Opioid With and Without an indication of Opioid Overdose, 2009-2016: Graphical representation of the bivariate analysis for diagnostic predictors

Table 4.11 shows the results of the multiple logistical regression analysis. Concomitant opioid and gabapentinoid administration increased the odds of overdose by 1.223 (95% CI: 1.014 – 1.476) when adjusting for demographic and diagnostic predictor variables. Gender was not a statistically significant predictor of overdose. When compared with white patients, black patients were at decreased odds of overdose (OR = 0.392; 95% CI: 0.307 - 0.500). Notable diagnostic measures which predicted an increased likelihood of overdose included Fibromyalgia (OR = 1.376; 95% CI: 1.146 - 1.652), seizures (OR = 2.253; 95% CI: 1.833 – 2.769), chronic pain (OR = 2.505; 95% CI: 2.029 – 3.092), mental health disorder (OR = 2.792; 95% CI: 2.036 – 3.092), and opioid abuse (OR = 5.549; 95% CI: 4.611 – 6.678). An opioid prescription which exceeded 120 MEDD increased the odds of overdose by 1.507 (95% CI: 1.126-2.017).

Table 4.11 Multivariate Logistic Regression of Opioid Overdose, Adjusting for Demographic, Diagnostic Predictors, SC Medicaid Recipients Prescribed Gabapentin With and Without a Concomitant Opioid Prescription

Characteristics	Adjusted OR (95% CI)	Model Statistic p value	Unadjusted OR (95% CI)	Model Statistic p value
Concomitant Gabapentinoid and Opioid Use	**1.223 (1.014 - 1.476)**	**0.0355**	**2.296 (1.935 – 2.724)**	**<0.0001**
Demographics				
Age				
18-29	1 [Reference]			
30-39	1.186 (0.875 - 1.607)	0.2725	1.619 (1.210 – 2.165)	0.0012
40-49	1.282 (0.956 - 1.719)	0.0967	2.435 (1.858 – 3.192)	<0.0001
50-64	1.144 (0.839 - 1.560)	0.3943	1.883 (1.423 – 2.490)	<0.0001
Male	0.987 (0.810 - 1.203)	0.8965	0.999 (0.830 – 1.202)	1.202
Race/ethnicity				
White	1 [Reference]			
Black	0.392 (0.307 - 0.500)	<0.0001	0.232 (0.183 – 0.293)	<0.0001
Hispanic	0.248 (0.034 - 1.785)	0.1732	0.133 (0.019 – 0.951)	0.0444
Other	0.642 (0.493 - 0.837)	0.0022	0.658 (0.509 – 0.849)	0.0013
Medicaid Information				
Qualifying Category				
AFDC	1 [Reference]			
Disabled	1.249 (0.670 - 2.327)	0.4845	2.476 (2.018 - 3.038)	<0.0001
Other/Unknown	1.943 (0.672 - 5.619)	0.2203	1.342 (0.546 – 3.296)	0.5217
Pay Category				
Low Income families	1 [Reference]			
SSI (Supplemental Security Income)	1.515 (0.816 - 2.813)	0.1880	2.427 (1.978 – 2.979)	<0.001

Aged, Blind, Disabled	1.928 (0.817 - 4.547)	0.1338	2.601 (1.395 – 4.850)	0.0026
Other/Unknown	0.956 (0.434 - 2.106)	0.9107	0.582 (0.295 – 1.148)	0.1184
Source				
FFS	0.824 (0.690 - 0.984)	0.0324	0.766 (0.648 – 0.905)	0.0018
Diagnosis Predictors				
Fibromyalgia	1.376 (1.146 - 1.652)	0.0006	2.774 (2.345 – 3.282)	<0.0001
Diabetic Peripheral Nerve Pain (DPN)	1.277 (0.964 - 1.692)	0.0882	1.558 (1.194 – 2.033)	0.0011
Seizures	2.253 (1.833 - 2.769)	<0.0001	3.172 (2.611 – 2.853)	<0.001
Restless Leg Syndrome	0.977 (0.645 - 1.480)	0.9122	1.878 (1.262 – 2.797)	0.0019
Chronic Pain	2.505 (2.029 - 3.092)	<0.0001	6.121 (5.069 – 7.392)	<0.0001
Mental Health Disorders	2.792 (2.036 – 3.092)	<0.0001	6.865 (5.074 – 9.288)	<0.0001
Opioid Abuse	5.549 (4.611 - 6.678)	<0.0001	11.793 (9.932-14.003)	<0.0001
Opioid Prescribing				
Opioid Prescription Exceed 120 MEDD	1.507 (1.126 - 2.017)	0.0058	2.177 (1.649 – 2.872)	<0.0001

CHAPTER 5

DISCUSSION

5.1 Summary of Findings

It is clear the use of gabapentinoids is rising in South Carolina's Medicaid population, with approximately 6.8% of all adult beneficiaries prescribed a gabapentinoid in 2016 up from 3.7% in 2009. This appears to be significantly higher than the general population. A recent study utilizing data from the Medical Expenditure Panel Survey (MEPS) found 3.9% of adults were prescribed a gabapentinoid in 2015 compared to the 6.3% found in this analysis during the same year (Johansen, 2018). This increase in individual level prescribing rates is consistent with the high number of gabapentinoid prescriptions being dispensed to Medicaid beneficiaries at South Carolina pharmacies. Gabapentin prescriptions were up nearly 400% from 23,204 in 2009 to 88,649 in 2016. However, pregabalin prescribing had little variation during the study period with approximately 10,000 prescriptions written each year of the study period.

The type of gabapentinoid appears to consistent with previously reported prescribing patterns. During the study period, gabapentin accounted for 84.6% of all gabapentinoid prescriptions written. This is consistent with the MEPS study finding of 82.6%. However, this trend has the potential to drastically change in

the coming years as pregabalin is anticipated to become available in a generic formulation during late 2019 and the preauthorization currently required for its prescribing to South Carolina Medicaid patients may change.

The most striking finding from Aim 2 was that approximately 60% of all patients prescribed a gabapentinoid during the study period had some overlap in prescribing days with an opioid, averaging between 73 and 86 days of overlap. Although average MEDD for opioid medications was decreasing during the study period (down from 57 MEDD in 2009 to 49 MEDD in 2016), Gabapentinoid daily dosages were found to be increasing. Gabapentin and pregabalin daily dosage were up 6.5% and 17.5% respectively from 2009 to 2016.

Consistent with previous investigations, it appear gabapentinoids are being routinely prescribed for off label use, with relatively few patients indicated for an FDA-approved condition when prescribed a gabapentinoid. Previous reports show that gabapentin is used for off-label indications in approximately 83% of prescribed patients (Radley, 2006). This analysis shows that even when gabapentinoids are being prescribed for approved indications, they often are coprescribed with an opioid, potentially resulting in increased risk for the patient. Only one of the four approved indications for a gabapentinoid investigated in this analysis showed decreased likelihood of concomitant prescribing (seizures). Patients with a history of fibromyalgia and diabetic nerve pain were in fact at increased likelihood of receiving both an opioid and a gabapentinoid. Patients with a history of restless leg syndrome were equally likely to receive either a gabapentinoid alone or a

gabapentinoid and an opioid concomitantly. The highest predictors of coadministration included chronic pain, a prescription for pregabalin, dosages exceeding recommended maintenance doses, and long-term use.

Surprisingly, a past history of opioid abuse and opioid overdose was not a predictor of coadministration. It appears that patients are receiving concomitant prescriptions for an opioid and gabapentinoid at similar rates, regardless of their past history of opioid abuse. Several documented studies point to the increased risk of gabapentinoid abuse when a previous history of substance abuse is indicated which makes this finding particularly troubling.

Aim 4 sought out to investigate whether concomitant opioid and gabapentin utilization resulted in adverse health outcomes. This study supports previous work which found concomitant treatment of gabapentin and opioid prescription increased the likelihood of opioid overdose (Gomes, 2017). This finding is indeed alarming due to the large number of individuals currently being coprescribed these medications. This study builds on the work of the Canadian based study by Gomes et al. by investigating a broader definition of gabapentinoids (both pregabalin and gabapentin) and adding an investigation utilizing a U.S. population to the growing body of literature.

5.2 Policy Implications

While the attention of the opioid epidemic still remains heavily focused on combatting illicit opioids such as heroin and reducing the number of prescriptions written for opioids, little federal attention has been given to the growing body of

evidence regarding gabapentinoid misuse and abuse. However, it is important to understand the potential for abuse and adverse drug events related to these medications which are being written in increasingly large numbers and routinely coadministered with opioids. State level efforts to ensure robust awareness and monitoring of these prescriptions should include:

Physician Education (general intervention)

A one-time letter should be dispensed to physicians who prescribe gabapentinoids regarding the medication's potential for abuse and increased likelihood of adverse drug events when coadministered with an opioid. These letters, often referred to as "Dear Colleague" or "Dear Doctor" letters are utilized by a variety of agencies (including SAMHSA, CMS, CDC, etc.) to keep providers up to date with new policies, best practices, and emerging topics in the field. "Dear Doctor" letters are a cost effective and timely first step in creating a dialogue with providers on the potential safety concerns of gabapentinoid and opioid co-prescribing.

It should be noted that several studies investigating changes in physician behavior following a 'Dear Doctor' letter campaign did not find significant differences (Weatherby, 2001; Theophile, 2011). When there was a significant change, the letters were found to be most effective if the information presented was simple and straightforward (Dstsch, 2014). The most dramatic changes to behavior were observed following a "Dear Doctor" letter campaign which utilized individualized letters informing

providers of a former patient's overdose death (Doctor, 2018). Following the receipt of the personalized letter, opioid prescribing decreased between 6.3% and 13.2%. This targeted approach may results in greater behavioral changes and could be considered for this intervention.

Increased Monitoring

Although there is increasing pressure to reschedule gabapentin at the federal level, gabapentin currently remains unscheduled. In an effort for greater oversight of prescribing rates and increased monitoring, several states have begun to reclassify gabapentin as a schedule V substance. Kentucky become the first state to reclassify gabapentin as a schedule V medication in 2017 amid growing reports of abuse in the state. Michigan, West Virginia, Tennessee have since followed their lead.

The main push for the reclassification of gabapentin as a schedule V medication for most states is the automictic mandatory reporting from pharmacies to the state run PDMP. However, South Carolina remains one of sixteen states to track only schedule II-IV medications in their PDMP, SCRIPTS. Consequently, the change in scheduling would do little to increase physician awareness or increase monitoring of the medication in South Carolina.

Therefore, the suggested approach is to add gabapentin and pregabalin medications to mandatory SCRIPTS reporting as a 'drug of concern' thereby helping physicians make informed decisions on

gabapentinoid and opioid prescribing while keeping the current DEA scheduling. Currently, Ohio, Virginia, Massachusetts, Minnesota, and Wyoming all require PDMP reporting of gabapentin, but have not alerted the scheduling of the medication. In the first month of monitoring data, Ohio found Gabapentin was the number one most prescribed medication of all substances being monitored, with a rate of nearly 30% more than then next most prescribed medication, oxycodone (MHAS Ohio, 2017).

Although the impact of state implemented scheduling changes to and PDMP reporting mandates for gabapentinoids is yet unknown, the newly available data will undoubtable make a meaningful impact to furture research investigating these medications.

Adding gabapentinoid medications to SCRIPTS reporting and monitoring will ensure physicians have more complete information when prescribing these medications. It will also allow state agencies to more accurately track prescribing trends and investigate changes year over year. By coupling this additional monitoring with increased physician awareness through a one-time letter campaign, further research can be conducted to ensure a comprehensive understanding of the benefits and risks of these medications. Careful monitoring of patients prescribed these medications especially when an opioid is coadministered is certainly warranted.

5.3 Limitations

It is important to highlight several limitations of this study. The results outlined in this analysis are limited to South Carolina Medicaid recipients only, which are disproportionally female, and may not be generalizable to other populations. However, this study did not find a significant difference between gender in any analysis and therefore the limitation is likely to have reduced impact to result interpretation and generalizability.

Secondly, the findings may not be generalizable to other Medicaid populations. South Carolina remains one of 14 states to have opted out of Medicaid expansion and the state ranks in the bottom quartile of overall health status in the nation (America's Health Rankings, 2018). However, the aim of this study was to investigate a population which may be at increased odds or receiving an opioid and gabapentinoid concomitantly and therefore will have implications to populations of similar risk.

Additionally, several limitations in the data set existed which warrant discussion. First, information on the prescribing physician was not available in the provided pharmacy files. As outlined in Chapter 2 physician characteristics such as specialty and location may explain variances in prescribing patterns and utilization. Secondly, variances in prescribing and overdoes due to urbanicity were unable to be explored due to a lack of reporting in the data set. Finally, the findings represent only patients who were prescribed and *filled* a gabapentinoid or

opioid prescription. Patients who were prescribed, but choose not to fill, their medication due to cost, time or other reasons were not captured in this dataset.

Despite the limitation listed above, this analysis gave a deeper insight into the prescribing patterns of gabapentinoids, coadministration with opioids, and the potential of negative health outcomes in a vulnerable population. This study provides a step forward toward filling the knowledge gap regarding these highly prescribed medications.

5.4 Future Work

This study provides a preliminary analysis to address the gaps in literature regarding gabapentinoid prescribing and the potential negative outcomes related to their coprescribing with an opioid. However, there are several opportunities to build upon this work. A geospatial analysis of the prescribing patterns utilizing county or zip-code level data could give further insight into potential variances which may be explained by local conditions such as urbanicity. This could lead to a more targeted intervention into especially vulnerable populations. Additionally, a study investigating prescribing changes following the 2017 mandate requiring all providers to check the state's PDMP program when prescribing CS II-IV medications is warranted to determine if prescribing of opioid alternative significantly increased.

5.5 Conclusions

Gabapentinoid prescribing in South Carolina's Medicaid has significantly increased in recent years. Concomitant prescribing of an opioid and a

gabapentinoid is extremely common and more likely when prescribed at higher dosages and for extended periods of time. Patients coprescribed an opioid and gabapentinoid appear to be at a higher risk of opioid overdose. Limiting the concomitant administration of these medications should be considered. When co-prescribing is deemed necessary, increased patient monitoring may be warranted for potential signs of misuse or abuse. Increasing physician awareness regarding the potential adverse effects of opioid and gabapentinoid concomitant administration, coupled with additional monitoring of gabapentinoids, is recommended to ensure safe prescribing of these medications.

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