Impact of Academic Detailing on Opioid Prescribing Among Primary Care Providers in the Chicagoland Region

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THESIS

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Pharmacy
in the Graduate College of the
University of Illinois at Chicago, 2019

Chicago, Illinois

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AUTHOR CONTRIBUTIONS

Chapter 1 of this dissertation is a literature review and summary of the opioid crisis, initiatives undertaken to address the opioid crisis, the current evidence on academic detailing and its impact on opioid prescribing, and the gaps in the literature intend to be addressed. My specific aims are outlined in this chapter. Chapters 2 through 4 represent three manuscripts prepared for submission to peer-reviewed journals on which I am the primary author and my other committee members are co-authors.

For the research in chapters 2,3,4, I developed the research questions, designed the study, wrote the protocol, conducted the analysis, interpreted the results, and drafted and edited the chapters. All committee members are co-authors on each manuscript. Each co-author has provided substantial and meaningful input into the research questions, study design, and presentation of results. Committee members also interpreted the results, commented on draft chapters and approved final versions of drafts for submission to the selected journals.

Chapter 5 of this dissertation summarizes the conclusions of my three specific aims, discusses the implications of this work, and provides recommendations for future research.

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LIST OF ABBREVIATIONS

AAPM	American Academy of Pain Medicine
AD	Academic Detailing
ADF	Abuse-Deterrent Formulation
APAP	Acetaminophen
APS	American Pain Society
BZD	Benzodiazepines
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CMO	Chief Medical Officer
CNCP	Chronic Non-Cancer Pain
CSA	Controlled Substances Act
DEA	Drug Enforcement Administration
DO	Doctor of Osteopathic Medicine
ED	Emergency Department
ER	Extended Release
FDA	Food and Drug Administration
FAQ	Frequently Asked Questions
HCPs	Hydrocodone-Containing Products
HEAL	Helping to End Addiction Long-term
IL PMP	Illinois Prescription Monitoring Program
IM	Intramuscular
IN	Intranasal
IR	Immediate Release
IV	Intravenous

LIST OF ABBREVIATIONS

JCAHO	Joint Commission on Accreditation of Healthcare Organizations
MAT	Medication-Assisted Treatment
MD	Doctor of Medicine
MME	Morphine Milligram Equivalent
NaRCAD	National Resource Center for Academic Detailing
NP	Nurse Practitioner
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OEND	Overdose Education and Naloxone Distribution
OUD	Opioid Use Disorder
PA	Physician Assistant
PCP	Primary Care Provider
PDMP	Prescription Drug Monitoring Program
PMP	Prescription Monitoring Program
REMS	Risk Evaluation and Mitigation Strategy
SC	Subcutaneous
SNRIs	Serotonin-Norepinephrine Reuptake Inhibitors
TCAs	Tricyclic Antidepressants
US	United States

SUMMARY

This dissertation examines the impact of an opioid-focused academic detailing (AD) program on controlled substance prescribing among primary care clinicians. Prescription and non-prescription opioid misuse and abuse is a major problem in the United States (US).[1] In 2017, the Centers for Disease Control and Prevention (CDC) reported more than 17,000 drug overdose deaths involved a prescription opioid.[2] Since clinicians in primary care specialties (e.g. family, internal, or general medicine) account for the majority of dispensed opioid prescriptions,[3,4] interventions that aim to modify opioid prescribing behavior should consider focusing their efforts on this subgroup of clinicians. These clinicians have reported inadequate pain management training which has impacted their ability to manage patients with pain.[5-7] Targeted education delivered through AD programs can be used to effectively modify prescribing behavior in this group of clinicians.[8] This dissertation includes five chapters that provides evidence on the impact of AD in modifying opioid and non-opioid controlled substance prescribing in primary care and offers practical considerations for policymakers, public health officials and researchers when developing, implementing, and evaluating educational outreach programs.

The first chapter provides a brief background to support the research questions of interest. The origins of the opioid crisis, efforts used to address the opioid crisis, and current evidence on the impact of AD in modifying opioid prescribing was summarized. The place in therapy for opioids and non-opioids in the management of chronic pain were highlighted. The efforts taken to facilitate safe and appropriate opioid prescribing and reduce opioid abuse resulting from increased opioid use were discussed. Literature support from the available evidence on the effectiveness of AD in modifying prescribing behavior was also provided. Finally, the gaps in the literature and justification for undertaking the research were also discussed in this chapter.

The second chapter of this dissertation is titled “Practice Change Intentions Align with

Opioid Prescribing Following Academic Detailing". This chapter aimed to assess the validity of

self-reported intention to change as a measure of actual behavior following an AD program. A quasi-experimental research design with a difference-in-differences (D-I-D) approach was used to compare pre-post changes in total opioid prescriptions and high-dose opioid prescriptions for clinicians who received AD and reported an intention to change versus those that reported no/low intention to change their practice behavior. In the intention to change group, the mean number of total opioid prescriptions per month per clinician declined by 1.48 (95% confidence interval [CI]: -2.48, -0.47) and the rate of high-dose opioid prescriptions per month per clinician declined by 0.50 (95% CI: -0.69, -0.31) compared to the no/low intention to change group following the AD program. This study showed alignment between self-reported practice change intentions and actual changes in opioid prescribing behavior. This finding suggests that a standardized single-item intention to change measure may be a valid immediate indicator of future prescribing behavior change following opioid-focused educational outreach programs.

The third chapter of this dissertation is titled “Secondary Effects of an Opioid-Focused Academic Detailing Program on Non-Opioid Controlled Substance Prescribing in Primary Care”. This chapter examined the potential secondary effects of an opioid-focused AD program on the prescribing of non-opioid controlled substances in primary care. A quasi-experimental research design with a D-I-D approach was used to compare pre-post changes in benzodiazepine (BZD), non-BZD sedative-hypnotic, and carisoprodol prescribing for clinicians who received AD visits (AD-exposed) versus a control group. There was no substantive change in the rates of non-BZD sedative-hypnotic and carisoprodol prescribing between the two groups. BZD prescribing declined in both groups, however at a lower rate in the AD-exposed group. The difference in the declining rates of mean monthly BZD prescriptions was higher by 0.73 (95% CI: 0.14, 1.31) in the AD-exposed group compared to the control group following the AD program. The higher relative rate of BZD prescribing in the AD-exposed group compared to the control group following the AD program may be reflective of an unintended consequence of opioid-focused

AD programs as clinicians learn to be cautious about opioid prescribing. These findings warrant further consideration and investigation prior to the large-scale implementation of opioid-focused educational outreach programs.

The fourth chapter of this dissertation is titled “Identification of Barriers to Safe Opioid Prescribing in Primary Care through Academic Detailing”. This chapter aimed to identify barriers to safe opioid prescribing in primary care. A qualitative analysis of cross-sectional data, collected in the form of field notes during the AD program, was conducted. Barriers to safe opioid prescribing were organized into the following six themes: 1) gaps in knowledge (n = 122); 2) lack of prescription monitoring program (PMP) utilization (n = 67); 3) patient pressures to prescribe opioids (n = 19); 4) insurance coverage policies (n = 12); 5) provider beliefs (n = 9); and 6) health system pain management practices (n = 5). These findings highlight barriers to safe opioid prescribing among a large group of primary care clinicians and supports the need for continued efforts to enhance pain management education and maximize PMP utilization.

The fifth chapter of this dissertation summarizes the findings and implications of the three studies that were conducted. The overall implications of this research are for future clinician-targeted, opioid-focused educational outreach programs 1) to consider utilizing standardized single-item intention to change measures as a potential immediate indicator of future prescribing behavior change following the program; 2) to incorporate targeted education on appropriate BZD prescribing into opioid-focused AD programs as a featured component; and 3) to leverage the AD visit to understand the scope of system-wide barriers clinicians encounter. The findings from this dissertation have been used to influence statewide legislation for mandatory prescriber education on opioid prescribing and secure funding from national and state agencies (i.e. CDC and IL PMP) to continue implementation and evaluation of opioid-focused AD programs across Illinois. Furthermore, these findings can be used to inform and guide policymakers, public health officials and researchers when considering development,

implementation, and evaluation of opioid-focused AD programs. Replication of the studies undertaken in chapters 2 through 4 may help to provide further evidence for the use of educational outreach as an approach to modify controlled substance prescribing amid the current drug overdose crisis in the US.

I. INTRODUCTION

1.1 Chronic Non-Cancer Pain in the United States

Chronic non-cancer pain **(**CNCP), defined as non-cancer pain that persists beyond three months,[9] is a substantial public health problem in the US.[10] Over 50 million American adults in 2016 were impacted by CNCP,[11] a two-fold increase from 2012 likely due to a growing elderly population.[12] CNCP is a leading cause of disability[10,13] and contributes to upwards of $600 billion (in 2010 dollars) annually in direct and indirect costs (i.e. lost productivity).[10] Expenditures for CNCP exceed those of cardiovascular disease, diabetes, and cancer combined.[14,15] Thus, CNCP represents an immense burden placed on the US healthcare system and therefore warrants necessary improvements in preventing, evaluating, and treating CNCP.[10]

CNCP generally falls into two categories, nociceptive (pain in response to a noxious stimulus)[16] or neuropathic (pain caused by disease or injury to the nervous system).[17] Causes of nociceptive pain include musculoskeletal conditions (e.g. back and limb pain) and inflammation.[18] In contrast, causes of neuropathic pain include conditions such as diabetes mellitus and post-herpetic neuralgia.[19] Guidelines developed for the treatment of these and other types of CNCP recommend a comprehensive pain evaluation to facilitate clinical decision-making when determining the best course of treatment.[20-22] The goal of treatment for patients with CNCP is not 100% elimination of the pain but to reduce suffering and improve function.[23]

Treatment options should be chosen based on a thorough evaluation of the source and type of CNCP a patient is experiencing. Among the many treatment options for CNCP, pharmacologic therapies continue to be the most widely used.[24] Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen (APAP), tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) are common non-opioid pharmacologic therapies used to manage CNCP.[25-29] Moreover, there is recent evidence to suggest that the benefit of CNCP is similar between non-opioid and opioid therapies.[30] This level of evidence was not

available to frontline clinicians 20 years ago, thus fostering an environment in which the heavy marketing of opioids was able to have its enormous impact. The availability of these data now creates an opportunity to address the problems marketing efforts and other contributory factors have had on the “worst drug crisis in American history”.[1]

1.2 The Opioid Epidemic in the United States: How Did We Get Here?

Opioid prescribing has markedly increased since 1999, tripling in the amount overall amount prescribed by 2015.[31] Similarly, more than 200,000 prescription opioid-related overdose deaths have occurred since 1999.[32] Over 17,000 prescription opioid-related overdose deaths occurred in 2016 alone,[33] a five-fold increase from 1999.[32] Additionally, about 2 million individuals in the US currently have a substance use disorder (addiction) associated with prescription opioids.[34] The yearly financial burden of prescription opioid-related overdose, abuse, and addiction is estimated to be over $78 billion.[35] Prescription opioid-related overdose, abuse, and addiction have had an alarming impact on the US and constitute the present opioid epidemic.

The beginning of the opioid epidemic is often traced back to a brief letter written by Porter et al. published in the *New England Journal of Medicine* in 1980 claiming the development of addiction rarely occurred with opioid therapy among hospitalized patients with no known history of opioid addiction.[36] Although little evidence was provided to support this claim, several subsequent publications cited the letter as evidence of addiction is rare in patients treated with opioids.[37] Among the publications citing the letter was Portenoy et al. in 1986 which concluded that prescribing of opioids for long-term use was safe to treat patients with CNCP with little worry of the risk for addiction.[38] Similar to Porter et al., the claim made by Portenoy et al. lacked evidence but was widely cited and touted to promote the use of opioids to treat CNCP.

Coincidentally, citations of the 1980 letter spiked in the mid 1990’s after the introduction

of OxyContin, an extended-release (ER) formulation of oxycodone HCl, by Purdue Pharma.[37] Purdue Pharma's aggressive and strategic marketing efforts throughout the late 1990's to influence physician's prescribing behavior fueled sales of OxyContin to exceed $1 billion in 2000, a 20-fold increase from 1996.[39] Sales representatives were incentivized by large monetary bonuses to increase OxyContin sales by identifying and targeting high prescribers of opioids across the US.[39] Among the physician specialties targeted were Primary Care Provider (PCPs) and by 2003 almost half of the physicians prescribing OxyContin were comprised of PCPs.[40]

Purdue Pharma also propelled opioid prescribing by providing financial support to many organizations influential in pain management such as the American Pain Society (APS), American Academy of Pain Medicine (AAPM), and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO, now known as The Joint Commission).[41] Not surprisingly thereafter, routine assessment of pain as the "fifth vital sign" was strongly endorsed in 1995 by the APS and would spark a shift in the pain management paradigm.[42] By 2000, other national organizations like JCAHO and Veterans Health Administration (VHA) championed the APS's stance on increased identification and treatment of pain, ultimately impacting how pain management was practiced across the country.[42,43]

In 1997, the APS published a white paper advocating the use of prescription opioids to treat CNCP.[44] However, physicians remained skeptical about the use of opioids to manage CNCP and were specifically concerned about the risk of addiction if opioids were used long-term.[45] In spite of available evidence-based published studies supporting the risk of addiction with prescription opioids[46-49], distortion of the addiction risk with prescription opioids was driven by Purdue Pharma's aggressive promotion of evidence–lacking studies by Porter et al. & Portenoy et al.[39] This misrepresentation of addiction risk aimed to alleviate prescribers concerns about the addiction risk with opioids. As a result, the liberal use of OxyContin and other

prescription opioids ensued, ultimately fueling the present opioid epidemic. The epidemic has led to efforts to improve opioid prescribing practices to mitigate the risk of prescription opioid abuse and overdose.

1.3 Efforts to Mitigate Prescription Opioid Abuse and Overdose

Many efforts have been undertaken to address prescription opioid abuse and overdose. Some of these efforts include abuse-deterrent opioid formulations, up-scheduling of hydrocodone-containing products (HCP), pill mill laws, naloxone access, medication-assisted treatment, coverage and reimbursement policies, PMPs, and enhanced provider education. The following sections provide examples of these efforts intended to reduce prescription opioid utilization, abuse, and overdose.

1.3.1 Abuse-Deterrent Opioid Formulations

The use of ER prescription opioid formulations, such as OxyContin, increased sharply during the late-1990's.[50] They were thought to be advantageous due to their lower potential for abuse relative to immediate-release (IR) formulations because of their delayed absorption and slow onset of action.[51] ER formulations were made to be swallowed whole, however, abusers rendered the ER mechanism useless by chewing the tablets, crushing the tablets to snort, or dissolving the tablets in water for injection.[52,53] By destroying the ER mechanism, a higher dose of the opioid is quickly released and absorbed. Escalating levels of abuse subsequently triggered manufacturers, beginning in 2010 with Purdue Pharma, to reformulate the opioid into an abuse-deterrent formulation (ADF) to be less susceptible to abuse by crushing, chewing, or dissolving.[54,55] Though cases of successful efforts to defeat the ADF mechanism were reported,[56] the impact of introducing an ADF for OxyContin was associated with a decrease of greater than 20% in its utilization a year after reformulation.[57] Although the use of OxyContin declined, abuse and misuse of non-ADF opioids remain a concern.

1.3.2 Up-scheduling of Hydrocodone-containing Products

Although reformulation of OxyContin to an ADF was associated with declines in its utilization, prescription opioid-related overdose deaths due to abuse or misuse continued to steadily climb well after its reformulation in 2010.[58] High utilization of other prescription opioids, like hydrocodone-containing products (HCPs) which contain either acetaminophen or ibuprofen, continued to be a driving factor for prescription opioid abuse and overdose.[50] By 2012, HCPs accounted for 25% (135 million prescriptions) of all dispensed prescription medications.[59] The alarming use and concern for abuse of HCPs prompted regulatory efforts by the Drug Enforcement Administration (DEA) to federally reschedule HCPs from schedule III to schedule II controlled substances in 2014.[60] By rescheduling HCPs from schedule III to schedule II, HCPs were now subject to stricter, more stringent controls such as 30-day supply limits and prohibition of refills for new prescriptions. Studies evaluating the impact of HCP rescheduling found an association with reduced rates of HCP prescribing greater than 20% between 2013 and 2015, however, rates of prescribing for non-HCP opioids modestly increased about 5% over the same timeframe, though not enough to offset the reduction in HCP prescribing. [61,62]

1.3.3 Pill Mill Laws

Due to large geographic variations in opioid prescribing rates, state and local policy strategies are often needed to reduce prescription opioid utilization, abuse, and overdose.[63,64] One notable example of an effective state policy to reduce opioid prescribing was the implementation of Florida's "pill mill" laws in 2010.[65] The term "pill mill" refers to any doctor, clinic, or pharmacy inappropriately prescribing and/or dispensing federally scheduled prescription drugs.[66] Pill mills in Florida manifested as revenue-driven pain clinics which grew rapidly from 2007 to 2009, eventually outnumbering common fast-food chains in some counties.[67] These pain clinics often inappropriately prescribed and dispensed large amounts of commonly abused prescription drugs, such as opioids and BZD, contributing to the 84% rise in prescription drug overdose deaths from 2003 to 2009.[68] The increasing number of pain clinics

and rise in prescription drug overdose deaths prompted Florida's creation of regulatory policies for pain clinics intended to curb improper prescribing practices and reduce the supply of prescription opioids. In 2010, Florida established "pill mill" laws to strictly regulate pain clinics and their prescribing practices and was associated with a 1.4% reduction in prescription opioid utilization and a 27% reduction in prescription opioid-related overdose deaths from 2010 and 2012.[65,69]

1.3.4 Naloxone Access

The increasing rates of overdose deaths involving prescription opioids warrant strategies aimed to prevent and reduce the risk of opioid overdoses, such as expanding access to naloxone.[70,71] Naloxone is a prescription opioid antagonist that rapidly reverses potentially fatal respiratory and central nervous system depression and may be administered via an intravenous (IV), intranasal (IN), intramuscular (IM), or subcutaneous (SC) route to individuals suffering an opioid overdose.[72] Naloxone has historically been administered by healthcare professionals in clinical settings or emergency medical personnel responding to emergencies. However, the distribution of naloxone for administration by non-healthcare professionals is becoming more common in response to increasing overdose rates.[70,73] From 1996 to 2014, community-based overdose education and naloxone distribution (OEND) programs (e.g. public health departments, substance use treatment facilities, etc.) expanded greatly from 188 to 644 programs, a 243% increase.[74] These programs provide training to drug users, their friends, and family members, and laypeople to promptly recognize and respond to an overdose. A systematic review of community-based OEND programs found high levels of participation to be associated with declines in overdose deaths, improved ability to recognize and respond to overdoses, and safe naloxone administration.[75]

As community-based OEND programs have proliferated over the past 20 years in response to the need for improved naloxone access, dispensing of naloxone from retail

pharmacies also grew. There was a 10-fold increase of naloxone dispensing from retail pharmacies from 2013 to 2015 with the majority of prescriptions accounted for by PCPs.[76] Efforts to further increase naloxone access through pharmacies include legal provisions allowing dispensing of naloxone via standing order. The standing order allows naloxone to be provided to individuals meeting criteria specified in the order, removing the need to obtain a prescription.[77] Many states have passed laws to permit dispensing of naloxone via standing order to anyone that may be at risk of an opioid overdose or to family members, friends, or caregivers of someone that may be at increased risk of an opioid overdose.[78] The impact of laws passed to permit dispensing of naloxone via standing order has been associated with significant increases in national naloxone dispensing. Specifically, there has been a 500% increase in the number of naloxone prescriptions dispensed from retail pharmacies from 2015 to 2016, the majority accounted for by direct prescriptions written by PCPs.[79] Current strategies are being explored by the FDA to increase access to naloxone through over-the-counter availability and/or co-prescribing naloxone with each opioid prescription written by prescribers.[80]

1.3.5 Medication-Assisted Treatment

Strategies to mitigate other risks associated with opioid use, such as opioid use disorder (OUD) which affects over 2 million people, including the development of improved treatments for patients with OUD.[81] Opioid use disorder is characterized as a problematic pattern of opioid use leading to clinically significant impairment or distress.[21] Medication-assisted treatment (MAT), such as buprenorphine, methadone or naltrexone, combined with behavioral therapies is recommended for patients who may be suffering from OUD. MAT has been demonstrated to be effective[82] and is associated with declines in prescription opioid use[83] and overdose deaths[84]. However, about half of the patients initiating MAT will relapse in six months.[85] Similarly, less than half of patients in addiction treatment programs with OUD receive MAT, supporting the need for improved access to MAT.[86] Therefore, initiatives like Helping to End Addiction Long-

term (HEAL) launched by the NIH in 2018 have allocated resources to conduct innovative research towards reformulation of current MATs to improve adherence, development of new MATs, and exploration of new care models to increase access to MATs.[85]

1.3.6 Coverage and Reimbursement Policies

Insurers, both public and private, and pharmacy benefit managers (PBMs), who process prescriptions for insurers, can play a vital role to reduce prescription opioid abuse and misuse by leveraging formulary coverage policies to influence opioid prescribing practices.[87] Formulary controls have been employed to reduce inappropriate opioid prescribing patterns and utilization.[88] These controls have included programs that review past drug utilization for inappropriate patterns of drug use and notify the clinicians about such use (i.e. drug utilization reviews), require medical justification prior to drug coverage (i.e. prior authorizations), and place limitations on quantities of drugs dispensed in a given time period (i.e. quantity limits). Similarly, non-opioid pharmacologic (e.g. prescription NSAIDs) and non-pharmacologic treatments (e.g. physical therapy) are also subject to policies that may limit access. While these treatments are recommended as initial pain management programs by evidence-based guidelines, the controls used for these treatments may pose significant barriers, which impedes their utilization. [89,90] Adoption of coverage policies consistent with evidence-based guidelines, such as step therapy requirements prior to opioid initiation, would incentivize initial use of non-opioid pharmacologic and non-pharmacologic treatments by clinicians. These policies may improve opioid prescribing practices and reducing opioid misuse and abuse.[89,91]

1.3.7 Prescription Drug Monitoring Programs

Prescription drug monitoring programs (PDMPs) are tools that can be used to improve opioid prescribing practices. PDMPs are statewide electronic databases that collect timely information from retail pharmacies on dispensing of schedule II through schedule IV or V controlled substance prescriptions (e.g. drug name, payment type, prescriber information,

etc.).[92] Thus, PDMPs can be used by clinicians to identify problematic controlled substance utilization behaviors, such as receiving multiple opioid prescriptions from multiple providers (i.e. doctor shopping), and support clinical decision-making to reduce prescription opioid misuse, abuse, and diversion.[93] Utilization of PDMPs can facilitate safe and appropriate opioid prescribing practices by determining if patients are receiving high opioid dosages (i.e. > 90 Morphine Milligram Equivalent [MME]/day) or dangerous combinations of prescription medications (i.e. concurrent opioid and BZD use) that may put them at increased risk for overdose.[21] Studies evaluating PDMP implementation have found PDMPs associated with modest reductions of 1-2% in opioid prescribing 12 months after implementation[65,94] but no association with reductions in drug overdose mortality.[95] These findings may be attributed to inconsistent PDMP use and variability in PDMP features (e.g., daily reporting by pharmacies, lack of data sharing between states, etc.).

Although there is evidence to suggest PDMPs may help improve opioid prescribing, the effectiveness of PDMPs relies on prescribers to access and review the database prior to prescribing controlled substances. However, prescribers have reported a lack of routine use of the PDMP even though many are aware of the PDMP and its utility.[96,97] Common barriers to PDMP utilization at the point of care include online registration and access difficulties, lack of time to access PDMPs, and lack of PDMP usability.[98,99] Additionally, a lack of clear guidance on how to proceed with the information found in PDMPs can also pose a barrier to PDMP utilization by clinicians. Recommended strategies to overcome these barriers encountered by prescribers include mandatory PDMP registration and use, integration of PDMPs with electronic medical records (EMR), and allowing delegates to access the PDMP on the prescriber's behalf.[99-101] Implementation of policies that promote PDMP use (i.e. mandatory PDMP registration and use) and ease prescriber time burden (i.e. delegate access of PDMP) has been associated with modest reductions in opioid prescribing by 6-10%[102,103] and prescription opioid overdose deaths

by 12%.[104] The impact of these policies suggests improved clinical decision–making and support continued efforts to facilitate PDMP access and usability (i.e. integration of PDMP with EMRs) to further reduce prescription opioid abuse and overdose. Furthermore, providing clinicians with clear and actionable recommendations (e.g. clinical practice guidelines) to follow based on information uncovered in the PDMP may also improve its utilization.

1.3.8 Provider Education

Despite the utility of PDMPs in facilitating improved opioid prescribing, clinicians have generally expressed a lack of comfort when using opioids to manage patients with CNCP due to inadequate knowledge and training related to prescribing opioids.[6,105] Clinical practice guidelines are traditional methods employed to improve the education of clinicians and motivate behavior change.[106,107] A 2014 systematic review of published opioid guidelines identified many similarities in strategies to reduce prescription opioid abuse and overdose, however the evidence supporting these guidelines had become outdated (e.g. previous evidence supported >200 MME/day = high risk for overdose; current evidence supports >90 MME/day = high risk for overdose).[108] Hence, in March 2016 the CDC released the *Guideline for Prescribing Opioids for Chronic Pain* which is a comprehensive, broad-reaching guideline intended to provide evidence-based recommendations to front-line clinicians for safe and appropriate opioid prescribing practices when managing patients with CNCP **(Table I)**.[21] The guideline was developed using the CDC Advisory Committee on Immunization Practices (ACIP) adaptation of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method.[109] The ACIP GRADE framework was used to assess the quality of the evidence and develop recommendations. The recommendations were classified as either Category A, which indicates that most patients should receive the recommended course of action, or Category B, which indicates that there should be individual decision making.

Table I. CDC Recommendations for Prescribing Opioids for Chronic Non-Cancer Pain

Recommendation	**GRADE Category***
1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate	A
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety	A
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy	A
4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids	A
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day	A
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed	A
7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids	A

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present	A
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months	A
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs	B
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible	A
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder	A
*GRADE categories were based on the following: • No evidence shows a long-term benefit of opioids in pain and function versus no opioids for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized trials ≤6 weeks in duration). • Extensive evidence shows the possible harms of opioids (including opioid use disorder, overdose, and motor vehicle injury). • Extensive evidence suggests some benefits of nonpharmacologic and nonopioid pharmacologic treatments compared with long-term opioid therapy, with less harm.	

While the guidelines provide evidence-based recommendations, managing patients with CNCP remains complex and prescribers must balance maximizing safe and appropriate opioid practices while avoiding undertreatment of pain and opioid abuse.[110] A recent study evaluating the changes in national opioid prescribing trends since the release of the CDC guidelines found an 8% monthly decline in the rate of high dose opioid prescribing (> 90 MME/day) and 0.08% monthly decline in the percentage of patients with overlapping opioid and BZD fills between

March 2016 to December 2017.[111] The release of the guideline is proposed to have contributed to improved opioid prescribing practices and suggests increased efforts to encourage the implementation of these guidelines.[111] An evidence-based strategy championed by the CDC as an effective method to increase uptake and implementation of current practice-based recommendations to improve prescribing behavior is clinician educational outreach via academic detailing.[112]

1.4 Academic Detailing

The Prescription Drug Overdose: Prevention for States (PfS) is a program funded by the CDC since 2015 which helps states battle the opioid overdose epidemic. The purpose of the PfS program is to support state agencies with resources to develop and initiate programs to mitigate prescription opioid misuse and abuse and ultimately preventing prescription drug overdoses. Thus, funded states, including Illinois, are collaborating with key partners (e.g. academic institutions) to implement and evaluate the impact of PfS activities. Maximizing PDMP use, state policy assessments, and community/health-system level programs are examples of PfS activities under evaluation. The CDC supports several evidence-based strategies to evaluate the impact of PfS activities on reductions in prescription opioid misuse, abuse, and overdose.[112] Among the supported strategies by the CDC is academic detailing.

Academic detailing, first described by Dr. Jerry Avorn, uses direct educational outreach to front-line clinicians to improve prescribing and other medical decisions by increasing the use of evidence-based practices.[8,113] AD uses specially trained personnel, usually healthcare professionals, to provide clinicians with unbiased, evidence-based information. It is delivered through individual face-to-face visits aimed at improving their decision-making and prescribing behavior.[8,113] Characteristics of AD generally include: 1) focused clinical education highlighting relevant key messages; 2) audit and feedback about clinical performance (e.g. clinician-specific prescribing information); 3) reputable, current, and unbiased (non-commercial) sources of

information (e.g. clinical guidelines); 4) recommendations about practice change; 5) identification of barriers to prescribing behavior change and facilitation of solutions to the identified barriers; 6) stimulation of active clinician participation during the visit; 7) a measure of intention to change prescribing behavior; and 8) succinct and clear educational materials (e.g. pamphlets).[113,114] Incorporation of these characteristics into AD programs is often done to effectively promote change in prescribing behavior and clinical decision-making.

1.4.1 Effectiveness of Academic Detailing on Modifying Prescribing Behavior

The effectiveness of AD is evaluated by measuring changes in clinical decision-making, knowledge, and prescribing behaviors. Results from a meta-analysis in a Cochrane review of 69 studies utilizing AD to modify prescriber behavior found this educational outreach strategy exhibited small but consistent improvements in prescribing behavior (median adjusted risk difference: 4.8%, interquartile range: 3.0% to 6.5%) after the educational outreach program.[115] AD has been applied to improve prescribing behavior related to antihypertensives,[116] antimicrobials agents,[117] alcohol use disorder treatment,[118] medication error reduction,[119] and HIV testing.[120] The improvement in clinical decision-making and prescribing behavior associated with AD supports its use as an evidence-based strategy to improve safe and appropriate opioid prescribing among PCPs. In 2018, the CDC championed AD as an evidence-based strategy to improve prescribing behavior related to opioids.[112] Studies utilizing AD to modify prescribing behavior related to opioids found associations of AD with modest reductions in prescription opioid-related mortality[121] and high-dose opioid prescribing.[122] Similarly, these AD studies also found modest improvements in adherence to opioid guidelines[123] and PDMP use [124,125] **(Table II).**

Table II. AD Studies on Prescribing Activities Related to Opioids

Study	N	Population	Study design	Program	Main Outcomes	Key Findings

Cochella et al., 2011[121]	581	Primary care physicians throughout urban and rural Utah	Quasi-experimental, pre-post comparison conducted from August 2008 to October 2009	Physician outreach detailing via group presentations highlighting recommended opioid prescribing practices to decrease deaths related to prescription opioids in Utah	Opioid-related deaths	Provider detailing was associated with a 14% decrease in Utah's prescription opioid death rate
Kattan et al., 2016[122]	1069	Physicians, NPs, and PAs with specialties likely to involve outpatient, non–	Quasi-experimental, pre-post comparison conducted from March 2013 to February	A 2-month public health detailing campaign (one-to-one educational visits) about judicious	Changes in total and high-dose (>90MME/day) opioid prescriptions	The program was associated with a significantly lower overall and

		end-of-life care (e.g internal medicine) from Staten Island, NY	2014	opioid prescribing among providers in Staten Island, NY. Non-detailed providers from the other NY boroughs served as the control group		high-dose opioid prescribing rates in Staten Island compared to other NY boroughs ($P < 0.01$)
Liebschutz et al., 2017[123]	53	Primary care clinicians (PCC) in 4 safety-net primary care practices in Boston, Massachusetts	Cluster-RCT conducted from January 2014 to March 2016	A multicomponent program (TOPCARE) including 1-on-1 AD, nurse care management, an electronic registry, and electronic	Guideline-concordant care over 12 months	At 1 year, Patients of program PCCs were more likely than patients of control PCCs to receive guideline-

				decision tools for safe opioid prescribing among program PCC. Control PCC received electronic decision tools only		concordant care (OR, 6.0; 95% CI, 3.6-10.2)
Barth et al., 2017[124]	87	Physicians in the VA and community practices in South Carolina	A single group, feasibility study conducted from September 23 to November 20, 2015	AD program to improve the use of the PDMP to improve safe opioid prescribing practices and prevent prescription opioid misuse	Feasibility and effectiveness of the pilot educational program to improve the use of the PDMP among physician prescribers	AD delivery and PDMP registration during the AD visit was effective at improving clinicians' knowledge and

						confidence regarding safe opioid prescribing practices
Larson et al., 2018[125] (follow-up study/analysis to Barth et al., 2017)	87	Physicians in the VA and community practices in South Carolina	Single group, pre-post comparison conducted from September 23 to November 20, 2015	AD program intended to increase the use of patient prescription history information from the state PDMP	Physician self-report of a patient prescription report query in the past 30 days utilizing the PDMP	Among 43 physicians who self-reported not using the PMP before the AD program, 83% self-reported adoption of PMP use after the AD program

1.4.2 Comparison of Self-Reported Intention to Change Opioid Prescribing Behavior with Actual Changes in Prescribing Behavior

The impact of AD on prescribing behavior cannot be evaluated immediately after the AD program has been delivered because of the length of time needed to accrue (e.g. 3-6 months) before observing an effect on prescribing behavior. Therefore, capturing self-reported intention to change prescribing behavior immediately after the AD visit concludes may provide an initial indicator of AD effectiveness. After an extended period of time has passed, the effectiveness of the AD program can be evaluated by comparing a provider's self-reported intention to change their behavior related to opioid prescribing with their actual prescribing data. Previous AD studies have not explored the agreement between self-reported intent to change and change in behavior. This comparison may provide valuable information that could be used to identify prescribers warranting further educational outreach and inform the development and delivery of future AD programs to improve their effectiveness. For example, providers who express an intention to change but do not may require practice facilitation to help implement the changes in which they are interested. Conversely, providers who do not express an intention to change prescribing behavior and continue to remain problematic prescribers (e.g. opioid prescriptions >90 MME/day, co-prescribing BZD and opioids, etc.) 3-6 months after the program, may warrant a "dose increase" via another AD visit or a different type of program. The additional AD visit may be conducted by the same or different detailer (if possible). The use of a different detailer may be necessary if the previous detailer is associated with providers consistently indicating their unlikeliness to change their prescribing behavior. This may be a possible reflection of poor performance by the detailer during the AD visit, providing an opportunity for quality assurance to examine the need for detailer re-training. By understanding the actual changes in prescribing, programs can be tailored to target prescribers who would be good candidates for additional AD visits. Similarly, identification of poor delivery of the AD program by the detailer may be identified which may offer an opportunity for re-training to ensure fidelity of AD program delivery. No known study exists comparing PCPs self-reported intention to change their opioid

prescribing behavior with actual changes in prescribing behavior.

1.4.3 Secondary Effects of Academic Detailing on Prescribing of Non-Opioid Controlled Substances

Secondary effects in program evaluation can be characterized as effects of a program (i.e. AD program) occurring beyond the scope of its intended purpose (i.e. improved opioid prescribing) and these effects are important to consider when estimating the impact of the program.[126] Prior AD studies focused on modifying opioid prescribing behavior have lacked assessment of potential secondary effects of the AD program on prescribing of non-opioid controlled substances with a high potential for misuse and abuse similar to opioids.

Use of non-opioid controlled substances like carisoprodol, BZD, and non-BZD sedative-hypnotics have sharply increased in parallel with prescription opioids.[127-129] Use of these drugs alone or in combination with opioids is associated with increased risks of abuse and opioid overdose death.[130-132] These drugs are reported in the PDMP in Illinois. Thus, providers might be more aware of their use as they access the PDMP. Increased access and awareness may lead to secondary effects of an AD program focused on appropriate prescribing of opioids and increased use of the PMDP as a tool to identify high-risk patient behavior. Evaluation of potential downstream effects of AD on improved prescribing of non-opioid controlled substances, with similar problematic prescribing patterns as opioids, may provide evidence of AD's ability to reach beyond its intended goal to improve opioid prescribing. These additional effects are important to consider when evaluating the overall benefit of an AD program. The first study evaluating AD incorporated an assessment of substitution effects which found no change in the use of substitute pain medications (NSAIDs or pentazocine) for the target pain medication (propoxyphene) clinicians were detailed on.[8] There are no known studies that have evaluated the change in prescribing patterns of non-opioid controlled substances following an AD program focused on prescribing activities related to opioids among PCPs.

1.4.4 Identifying Primary Care Provider-reported Barriers to Safe and Appropriate Opioid Prescribing

Educational outreach via AD visits may serve as an adequate vehicle to elicit barriers from clinicians.[133,134] The engagement between the detailer and clinician during the AD visit provides an opportunity to identify potential barriers related to opioid prescribing. Leveraging the AD visit as a tool to identify barriers reported by PCPs related to safe and appropriate opioid prescribing when treating patients with CNCP can heighten the support of the national, state, and system-level policies and initiatives to address barriers and facilitate improved opioid prescribing behavior.

Prior studies identifying barriers clinicians encounter when managing patients with CNCP used focus groups/semi-structured interviews and were conducted with PCPs from the VHA.[133,134] Utilizing VHA-PCPs potentially reduces the generalizability of findings to non-VHA PCPs due to patient mix and standardized internal approaches to pain management which may be lacking other large non-VHA health systems. Specifically, among published educational outreach studies focused on improving prescribing activities related to opioids, one study by Barth et al.[124] captured and reported barriers that may preclude opioid prescribing behavior change, however, the reported barriers were specific to PDMP utilization among VHA and non-VHA PCPs.[124] No known study exists which comprehensively examines barriers (e.g. clinical, health-system/administrative, and technology issues related to pain management) encountered by non-VHA PCPs when treating patients with CNCP.

1.5 Gap in Literature

Change in prescribing behavior after an AD program requires a period of time (e.g. 3-6 months) to pass before evaluating the impact of the AD program. In lieu of time accruing after the AD program, eliciting a prescriber's intention to change their prescribing behavior immediately after the AD program can be used as a proxy for the AD program's effectiveness

and subsequent impact on prescribing. Previous AD studies have not compared a prescriber's intention to change prescribing behavior with their own prescribing data. Therefore, this study may provide valuable information to identify prescribers warranting further educational outreach and to inform the development and delivery of future AD programs (described above in 3.4.3.3). No known study exists comparing PCPs self-reported intention to change their opioid prescribing behavior with actual changes in prescribing behavior after receiving an AD program focused on prescribing activities related to opioids.

AD programs have been demonstrated to improve prescribing behavior specific to the purpose of the AD program. Thus, with the sharp rise in prescribing of carisoprodol, sedative-hypnotics, and BZD in parallel with opioids, it is not unreasonable to consider that an AD program focused on safe and appropriate prescribing of opioids may also impact more appropriate prescribing of these controlled substances. No known study has evaluated potential secondary effects of an AD program focused on safe and appropriate prescribing of opioids on the prescribing of non-opioid controlled substances.

Among published studies identifying barriers providers encounter related to pain management, identifying barriers non-VHA PCPs encounter is largely lacking. Additionally, the utility of the AD visit as a vehicle to capture the barriers encountered by non-VHA PCPs via one-on-one, face-to-face engagement will also be highlighted. This study can help to fill the gap regarding barriers non-VHA PCPs encounter when treating patients with CNCP.

1.6 Study Aims

The purpose of this dissertation was to understand the impact of an AD program focused on prescribing activities related to opioids among PCPs. Three study aims were developed to address the gaps in literature: 1) to compare self-reported intention to change and actual opioid prescribing behavior following an AD program; 2) to evaluate the secondary effects of an opioid-focused AD program on non-opioid controlled substance prescribing in primary care; and 3) to

identify barriers to safe opioid prescribing among PCPs through AD.

1.7 Conceptual Framework

No frameworks have been developed and published specifically relating to AD and its mechanism influencing prescribing behavior change. The proposed conceptual framework is adapted from the COM-B system **(Figure I).**[135] Its components are based on a behavior system involving capability (C), opportunity (O), motivation (M), and their interaction to generate behavior (B) change. Capability is defined as the individual's capacity to engage in the activity concerned including having the necessary knowledge and skills, opportunity is defined as factors that lie outside the individual that make the behavior possible or prompt it, and motivation is defined as processes that direct behavior, including habitual processes, emotional responding, and analytical decision-making.[135] The conceptual framework for the dissertation is illustrated in **Figure II** and was adapted to include an additional component, unintended behavior (gray), to reflect the hypothesized relationship between intended behavior change and unintended behavior change. This adaptation was made due to the evaluation of secondary and/or unintended effects of an AD program focused on safe and appropriate prescribing activities related to opioids (intended behavior) on the prescribing of non-opioid controlled substances (unintended behavior).

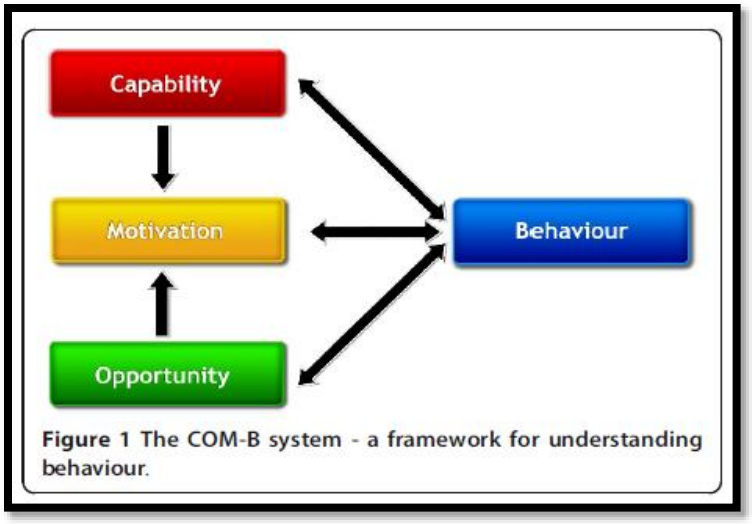

Figure I. COM-B System

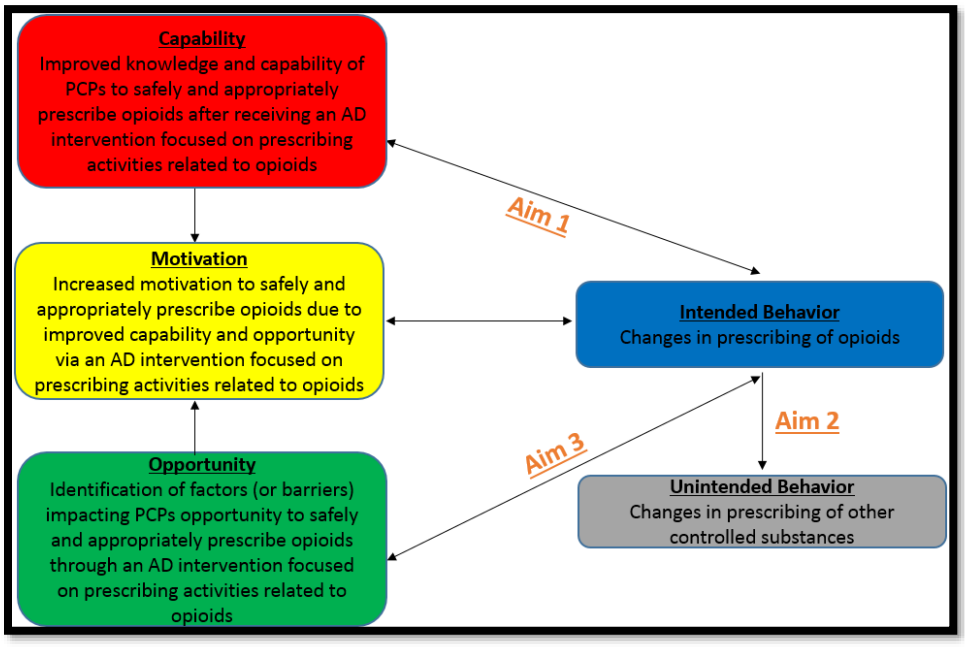

Figure I. Conceptual Framework

Aim 1 of the dissertation compared clinician self-reported intention to change and actual opioid prescribing behavior following an AD program focused on enhancing their capability to safely and appropriately prescribe opioids.

Aim 2 of the dissertation evaluated potential unintended/additional changes in prescribing patterns of non-opioid controlled substances after receiving an AD program focused

on enhancing PCPs capability to safely and appropriately prescribe opioids, the intended behavior change.

Aim 3 of the dissertation identified barriers reported by PCPs (e.g. lack of use/usability of the IL PMP, clinical knowledge gaps related to pain management, etc.) that impact their opportunity to practice safe and appropriate opioid prescribing behavior when treating patients with CNCP.

1.8 Academic Detailing Program on Opioid Prescribing among Primary Care Provider in the Chicagoland Region

Funding through the PfS program to Illinois facilitated a partnership between the Illinois Department of Human Services (DHS), IL PMP, and researchers at the University of Illinois at Chicago in the Department of Pharmacy Systems, Outcomes and Policy (UIC-PSOP) to evaluate the impact PfS activities. One key strategy in the Illinois PfS program includes the implementation and evaluation of community/health-system level programs. This key area led to an interest in evaluating the impact of AD. Since AD is an effective way to improve clinical decision-making and prescribing behavior, an AD program was developed to provide PCPs with information on the *Guideline for Prescribing Opioids for Chronic Pain*. The AD program was implemented through a partnership with AMITA Health Medical Group (AMITA), the third-largest hospital system in Illinois, with a network of more than 450 primary and specialty care providers serving Chicago's northwest, west and southwest suburbs.

1.8.1 Academic Detailing Program

The program group comprised of licensed healthcare professionals with prescriptive authority such as Doctors of Medicine (MD), Doctors of Osteopathy (DO), nurse practitioners (NP) and physician assistants (PA), with a focus on PCP specialties (e.g. internal or family medicine). Of note, prescriptive authority for controlled substances may be delegated to mid-level providers (i.e. NP and PA) via a written collaborative agreement with a physician (i.e. MD

or DO) who has a valid and up-to-date controlled substance license and federal registration in Illinois. Medication orders by the mid-level provider are reviewed periodically by the collaborating physician.

The AD program was delivered from June 2018 through August 2018. The program consisted of two one-on-one visits with the PCP and a trained detailer (i.e. first and second-year Doctor of Pharmacy and graduate students). The second AD visit occurred approximately six to eight weeks after the initial visit. Both visits were expected to last about 15 minutes in duration. The visits included the following components: 1) reviewing six key messages from the CDC *Guideline for Prescribing Opioids for Chronic Pain*; 2) providing PCP-specific information on past opioid prescribing from the IL PMP; 3) administering a survey on PCP satisfaction with AD visits; and 4) providing additional resources to facilitate safe and appropriate opioid prescribing practices (e.g. IL PMP informational brochure, Illinois Naloxone Standardized Procedure, etc.) **(Table III)**. These visit components align with the components of the COM-B model through enhancing PCPs capability and knowledge related to safe and appropriate opioid prescribing which may then motivate PCPs to improve their opioid prescribing behavior.

Table III. AD Visit Components

CDC GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN KEY MESSAGES
• Check PDMP for high dosages and prescriptions from other providers **(Recommendation # 9)** • Avoid concurrent benzodiazepine and opioid prescribing **(Recommendation # 11)** • Opioids are not first-line or routine therapy for chronic pain **(Recommendation # 1)** • Start low and go slow **(Recommendation # 5)** • Incorporate strategies to mitigate risk factors for opioid-related harms **(Recommendation # 8)** • Offer treatment for opioid use disorder **(Recommendation # 12)**
OPIOID PRESCRIBING METRICS
• **Provided at Visit 1** o Average number of monthly IL PMP queries o Average number of monthly opioid prescriptions o Proportion of opioid prescriptions by MME/day category (i.e. <50 MME/day, 50-89 MME/day, and >90 MME/day) • **Provided at Visit 2** o Average daily supply/opioid prescription o Average daily MME/opioid prescription o Average monthly number of patients co-prescribed opioids and benzodiazepines
PROVIDER SATISFACTION SURVEY **(response options: not at all, slightly, moderately, very, extremely)**
• The detailer was knowledgeable • The detailer was an effective communicator • Academic detailing is an effective way to get updated on important topic(s) • The printed material was useful • I would be receptive to future visits • This topic was relevant to my practice • This is an important topic • The key messages are feasible to implement in my practice • My practice is likely to change as a result of this visit • The key messages were consistent with my practice
ADDITIONAL RESOURCES
• Illinois Prescription Monitoring Program informational brochure • Illinois Naloxone Standardized Procedure • Illinois Opioid Treatment Program Directory • CDC Opioid Prescribing Guideline Mobile App • CDC *Guideline for Prescribing Opioids for Chronic Pain* • Alosa Health patient tear-off sheet – “What you should know about prescription opioids for short-term pain” • Evzio (naloxone HCl) Patient support program enrollment forms* • Responses to Frequently to Asked Questions Asked Questions From PCPs Related to Management of Patients With Chronic Pain* • Naloxone Access and Affordability Information/EMR vs IL PMP clarification*

1.8.2 Key messages from the CDC Guideline for Prescribing Opioids for Chronic Pain

The basis of AD is delivery of unbiased, evidence-based information; therefore, the CDC *Guideline for Prescribing Opioids for Chronic Pain* was used to develop the educational content for the AD program. The CDC *Guideline for Prescribing Opioids for Chronic Pain* has 12 total recommendations; however, it was considered infeasible to cover all 12 recommendations with PCPs due to time constraints for each visit. Therefore, AMITA leadership (e.g. Chief Medical Officer [CMO]) and external content experts, which consisted of physicians and pharmacists with extensive training in pain management in the Chicagoland area, were consulted to evaluate the most essential recommendations to include in the AD program. Ultimately, six key messages were selected to include in the AD program **(Table III).**

1.8.3 Opioid Prescribing Metrics

Audit and feedback is a widely used strategy to motivate behavior change. This strategy is based on the belief that when providers are given feedback on their performance showing that their clinical practice is not consistent with a desirable target they are prompted to modify their behavior.[136] Results of a meta-analysis from a Cochrane review of 140 studies utilizing audit and feedback to improve professional practice found this strategy resulted in small improvements in professional practice (median adjusted risk difference: 4.3%, interquartile range: 0.5% to 16%). Providing audit and feedback about the PCPs clinical performance via provider-specific prescribing information may aid in improved prescribing behavior.

Thus, PCP-specific opioid prescribing data were obtained from the IL PMP. At each of the AD visits, the PCPs were given information on their opioid prescribing patterns from November 2017 – April 2018 as well as the same opioid prescribing data for two comparison groups over the same time period. The comparison groups were other PCPs at AMITA and all prescribers in Cook County. The prescribing data for the Cook County providers was unadjusted for provider specialty since that information is not contained in the IL PMP database. There was

no “target” opioid prescribing goal presented to PCPs, however best practices per the CDC *Guideline for Prescribing Opioids for Chronic Pain* were emphasized during each visit. The specific opioid prescribing metrics provided at the AD visits are shown in Table III above.

1.8.4 Provider Satisfaction Survey

A provider satisfaction survey was created for the providers to give feedback about the detailer, the AD program and its impact on their practice. The survey also allowed the UIC-PSOP research team to immediately evaluate the detailer’s performance and effectiveness of the AD program.

A structured literature search was conducted using keywords related to provider satisfaction with AD and educational outreach to identify relevant constructs and measures of satisfaction for review. The constructs identified included: acceptability, feasibility, usefulness, perception of efficacy, overall satisfaction with the quality of the visits, and willingness to repeat the experience. After identifying relevant constructs, candidate items and response scaling options were generated. External content experts reviewed the items for content validity and wording. From these constructs, eight initial items were developed. After expert consultation, two items, including an item related to provider willingness to change, were added. The final version of the instrument used for the AD program contained 10 items **(Table IV)**. The instrument was administered at the conclusion of each AD visit. During survey administration, detailers removed themselves from the area where the AD visit took place to provide the PCP with privacy to reduce the potential for social desirability bias. Once the survey was completed, the PCP was instructed to place the survey in an envelope, seal it and return it to the detailer.

Table IV. Provider Satisfaction Survey

	Response options				
Item/Question	**Not at all**	**Slightly**	**Moderately**	**Very**	**Extremely**
The detailer was knowledgeable					
The detailer was an effective communicator					
Academic detailing is an effective way to get updated on important topic(s)					
The printed material was useful					
I would be receptive to future visits					
This topic was relevant to my practice					
This is an important topic					
The key messages are feasible to implement in my practice					
My practice is likely to change as a result of this visit*					
The key messages were consistent with my practice					

1.8.5 Additional Resources

Several additional resources were available to the detailers to share with PCPs at the visit. These were intended to supplement or enhance the key messages from the CDC Guideline. The additional resources included detailed instructions on the use of the IL PMP, information about a CDC opioid prescribing mobile app, a patient resource sheet concerning the treatment of acute pain, information on the Illinois standing order for naloxone, and a list of

opioid use disorder treatment programs **(Table III).**

Additional resources that were available for detailers to share at the second visit were developed based on concerns raised by the PCPs at the initial visit. These included concerns regarding clinical questions related to pain management, the IL PMP, and administrative/health–system issues. The UIC-PSOP research team worked in collaboration with AMITA leadership to address frequently asked questions (FAQ) by PCPs related to clinical practice (e.g. naloxone, non-pharmacologic treatment alternatives to opioids, etc.) and administrative/health–system matters (e.g. legal ramifications if uncomfortable prescribing opioids to a patient). AMITA leadership provided responses to several of these FAQs which were disseminated to PCPs on the second AD visit. Additionally, AMITA leadership provided AMITA-specific resources to distribute to PCPs receiving a second visit (e.g. outpatient pain management center contact lists and patient-facing materials for safe and appropriate use of opioids and naloxone). Another resource provided at the second AD visit was an informational guide on the pricing of the nasal spray and auto-injector formulations of naloxone. Information on a patient support program for the naloxone auto-injector formulation, Evzio, was also included as an additional resource. Lastly, an informational guide was developed and disseminated to clarify potential confusion around the ability of AMITA's electronic medical record (EMR) to access the IL PMP website.

1.8.6 Institutional review board

The University of Illinois at Chicago (UIC) institutional review board (IRB) and CMO at AMITA approved this study and informed consent was obtained from all participants.

1.8.7 Funding

This research was funded in part by the CDC Grant #1U17CE002739-01.

II. PRACTICE CHANGE INTENTIONS ALIGN WITH OPIOID PRESCRIBING FOLLOWING ACADEMIC DETAILING

2.1 Preface

This chapter addresses Aim 1 of the dissertation. It will be submitted for publication in a peer-reviewed journal as an article titled “Practice Change Intentions Align with Opioid Prescribing Following Academic Detailing”. The version for initial submission is presented here.

2.2 Introduction

Academic detailing is an educational outreach strategy that provides clinicians with current, unbiased, evidence-based information to improve their prescribing behavior and clinical decision-making.[8] AD is typically delivered by specially trained personnel (i.e. detailers) to clinicians through individual, face-to-face visits.[113] Behavior change is a common outcome when evaluating the effectiveness of AD programs.[137] Changes in behavior are typically measured using self-reported behavior change information collected from clinicians months to years following the AD program.[121,125,138-142] The clinicians’ self-reported behavior change is then used as a measure of the AD program’s impact on clinician behavior. However, the relationship between self-reported behavior change and actual behavior change is inconclusive.[143] Similarly, evidence on the agreement between clinician self-reported intention to change and actual behavior change is also unclear and warrants further investigation.[144] Since clinician self-reported changes in behavior are collected well after the AD program has ended, the impact of the program on clinicians’ actual behavior is not known right away. Thus, collecting information on practice change intentions via self-report from clinicians immediately after the AD program may be useful to provide an initial indicator of the program’s effect on behavior.

Academic detailing is endorsed by the CDC as an evidence-based strategy to combat the opioid crisis.[112] Therefore, many contemporary AD programs have incorporated evidence-based guidelines on safe opioid prescribing practices to facilitate improved opioid prescribing

behavior.[121-125,145,146] Among these programs, only two collected clinician self-reported changes in behavior months after the AD program to use as a measure of actual opioid prescribing behavior.[121,125] Opioid-focused AD programs have yet to explore the alignment between clinician self-reported intentions and actual opioid prescribing behavior following AD programs. Increased understanding of this relationship may provide evidence to support the validity of self-reported intention to change as a proxy measure of actual behavior following an AD program. The objective of this study was to evaluate the relationship between a self-reported intention to change item and actual changes in opioid prescribing behavior following an AD program.

2.3 Methods

A quasi-experimental pre-post study was conducted to compare clinician self-report of intention to change opioid prescribing to those clinicians' actual changes in total opioid prescribing and high-dose opioid prescribing following an AD program focused on safe opioid prescribing practices. Primary care clinicians who received an AD program from June 2018 to August 2018 and reported practice change intentions during the AD program were included in the study sample. The measured outcomes included monthly data on total opioid prescriptions and high-dose prescriptions were obtained from the IL PMP. Changes in monthly total opioid prescriptions and high-dose prescriptions obtained from the IL PMP were compared using a D-I-D approach to assess concordance with self-reported intention to change. These outcomes were measured for six months before the AD program (December 2017 to May 2018) and for six months after the conclusion of the AD program (September 2018 to February 2019) then compared between the groups. The institutional review board at the UIC approved this study. Informed consent was obtained from all clinicians who received the AD program, and no compensation was provided for participation in the study.

The AD program was implemented within a large health system in the Chicago metropolitan area from June 2018 to August 2018. The AD program consisted of two scheduled

face-to-face visits between clinicians and specially trained detailers. The visits were conducted at the health system's immediate care/walk-in clinics and were approximately 15 minutes in length. Components of the AD program are summarized in **Table III**. The AD program included six key messages from the CDC Guideline for Prescribing Opioids for Chronic Pain,[21] personalized opioid prescribing metrics obtained from IL PMP, and a single-item measure of the clinicians' practice change intentions (i.e. "My practice is likely to change as a result of this visit"). Response options for this item included "Not at all", "Slightly", "Moderately", "Very", or "Extremely".

Clinicians were included if they were licensed healthcare practitioners with prescriptive authority, such as MD, DO, NP, and PA, and practiced in primary care (i.e. family medicine or internal medicine) during the study period. Pediatricians and resident physicians were excluded. Clinicians who received the AD program and self-reported "Very" or "Extremely" were grouped as clinicians with an intention to change. Clinicians who self-reported "Not at all", "Slightly", or "Moderately" were grouped as clinicians with no/low intention to change. Baseline characteristics (i.e. sex, clinician specialty, clinician type, and years of practice) were collected directly from clinicians during the AD visits.

The outcomes indicating prescribing practice change were mean monthly number of total opioid prescriptions and mean monthly number of high-dose opioid prescriptions (>90 morphine milligram equivalents (MME)/day) per clinician. These outcomes were measured in the pre-AD program period (December 2017 to May 2018) and compared with outcomes measured in the post-AD program period (September 2018 to February 2019) between the intention to change and no/low intention to change groups.

Baseline characteristics for the clinician groups were compared using the chi-square test for categorical variables and the *t*-test to compare differences in means for continuous variables. Pre-post changes in outcomes between clinician groups were evaluated using a D-I-D

approach. [147] Repeated measures linear regression models were used with an unstructured covariance structure and a random effect for each clinician to account for correlation in the outcome measures within each clinician. Main effect terms were included in the model for binary indicators of AD exposure (yes or no) and the AD program period (pre or post). An interaction between the main effect terms represented the effect of the AD program on the outcomes. The interaction term, more specifically, represented the pre-post difference in the prescribing outcomes between the intention to change group and the no/low intention to change group. Individual clinicians were compared with themselves before and after the AD program. Therefore, baseline characteristics were not adjusted for in the model since they were considered time-invariant.

Since self-reported practice change intentions may be influenced by past prescribing behavior, subgroup analyses were conducted among clinicians with opioid prescribing data in the pre-AD program period. For total opioid prescriptions, the sample was restricted to clinicians who prescribed at least one opioid prescription in the pre-AD program period. For high-dose opioid prescriptions, the sample was restricted to clinicians who prescribed at least one high-dose opioid prescription in the pre-AD program period.

The results from the D-I-D analyses were presented as the mean monthly per clinician change in the outcome, represented by the D-I-D estimator as the model interaction term, and corresponding 95% CI. A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.: NC, Cary).

2.4 Results

In total, 149 clinicians were included for analysis **(Table V).** There were 72 clinicians in the intention to change group and 77 clinicians in the no/low intention to change group. Clinicians were mostly female (58.4%), physicians (82.5%), family medicine specialty (76.5%), and practiced for a mean of 17.5 years. No differences were significant among the baseline

characteristics between the groups.

Table V. Study 1 - Clinicians' Baseline Characteristics

There were no significant differences in the pre-post mean monthly number of total

Characteristic	Overall		Intention to Change		No/low Intention to Change		*p*
Total clinicians, n	149		72		77		
Sex, n (%)							
Female	87	(58.4%)	41	(56.9%)	46	(59.7%)	0.73
Male	62	(41.6%)	31	(43.1%)	31	(40.3%)	
Years of Practice, mean (SD)	17.5	(11.2)	17.4	(12.1)	17.6	(10.5)	0.89
Clinician Type, n (%)							
MD	85	(57.0%)	41	(56.9%)	44	(57.1%)	0.40
DO	38	(25.5%)	18	(25.0%)	20	(26.0%)	
NP	18	(12.1%)	11	(15.3%)	7	(9.1%)	
PA	8	(5.4%)	2	(2.8%)	6	(7.8%)	
Clinician Specialty, n (%)							
Family Medicine	114	(76.5%)	55	(76.4%)	59	(76.6%)	0.97
Internal Medicine	35	(23.5%)	17	(23.6%)	18	(23.4%)	

opioid prescriptions per clinician within the intention to change group (19.78 vs. 19.31, $p = 0.74$) and within the no/low intention to change group (11.15 vs. 12.16, $p = 0.33$). The mean monthly number of high-dose opioid prescriptions per clinician were significantly lower in the post-AD program period within the intention to change group (1.26 vs. 0.69, $p = 0.01$), however there were no significant differences in the pre-post mean monthly number of high-dose opioid

prescriptions per clinician within the no/low intention to change group (0.49 vs. 0.42, *p* = 0.27).

In primary D-I-D analyses, the intention to change group had a 1.48 (95% CI: -2.48, -0.47) reduction in the mean monthly rate of total opioid prescriptions and a 0.50 (95% CI: -0.69, -0.31) reduction in the mean monthly rate of high-dose opioid prescriptions per clinician compared to the no/low intention to change group **(Table VI)**. In restricted D-I-D subgroup analyses, the intention to change group (N = 71) had a 1.49 (95% CI: -2.53, -0.44) reduction in the mean monthly rate of total opioid prescriptions per clinician compared to the no/low intention to change group (N = 72) **(Table VI)**. The intention to change group (N = 39) had a 0.92 (95% CI: -1.31, -0.55) reduction in the mean monthly rate of high-dose opioid prescriptions per clinician compared to the no/low intention to change group (N = 33).

Table VI. Summary of Pre-Post AD Program Mean Monthly Prescribing Statistics and Difference-in Differences (D-I-D) Results for Intention to Change vs. No/low Intention to Change

	Intention to Change			**No/low Intention to Change**			**D-I-D**	**(95% CI)**	**D-I-D restricted subgroups**	**(95% CI)**
	Pre	**Post**	Δ	**Pre**	**Post**	Δ				
Total opioid prescriptions	19.78	19.31	-0.47	11.15	12.16	1.01	-1.48*	(-2.48, -0.47)	-1.49*	(-2.53, -0.44)
High-dose opioid prescriptions	1.26	0.69	-0.57*	0.49	0.42	-0.07	-0.50*	(-0.69, -0.31)	-0.92*	(-1.31, -0.55)

***p*-value < 0.05

Δ **=** represents the pre-post difference in the prescribing outcomes within the intention to change group and the no/low intention to change group

D-I-D = represents the pre-post difference in the prescribing outcomes between the intention to change group and the no/low intention to change group

D-I-D restricted subgroups = represents the pre-post difference in the prescribing outcomes between the intention to change group and the no/low intention to change group among subgroups of clinicians with opioid prescribing data in the pre-AD program period

2.5 Discussion

To determine the validity of self-report as a proxy measure for actual behavior following opioid-focused AD programs, it is important to explore the concordance between self-reported intention to change and actual opioid prescribing practices following the AD program. Therefore, changes in opioid prescribing practices were compared between primary care clinicians who self-reported intention to change and no/low intention to change their practice behavior after receiving an AD program that was focused on safe opioid prescribing. The intention to change group experienced a significantly lower change in the mean monthly rates of total opioid prescriptions and high-dose opioid prescriptions compared to the no/low intention to change group. These findings were consistent when restricting to clinicians with opioid prescribing data in the pre-AD program period. Overall, this study demonstrates alignment between self-reported practice change intentions and actual opioid prescribing behavior following an AD program.

Our findings suggest clinicians' self-reported intention to change practice behavior may be a valid indicator of actual behavior following the AD program; however, further research is needed to establish the validity of this relationship. The higher magnitude of total opioid and high-dose opioid prescriptions per month in the baseline period among the intention to change group relative to the no/low intention to change group was striking. The higher baseline prescribing rates among clinicians in the intention to change group may be indicative of clinicians who may warrant practice behavior change and benefit most from the opioid-focused AD program which may explain the significant reductions in prescribing observed in this study. Further, a lower baseline prescribing rate among clinicians in the no/low intention to change group would be expected, as there is less opportunity to improve given their lower initial baseline level of prescribing.

The results of this study add to limited evidence on associations between clinicians' self-reported intentions and actual behavior change following programs aimed to modify their

prescribing behavior and clinical decision-making.[143,144] Clinicians who self-reported an intention to change their practice behavior following receipt of the AD program subsequently experienced lower changes in the rates of total opioid prescribing and high-dose opioid prescribing relative to clinicians who self-reported no/low intention to change based on prescribing data from the IL PMP. These results translate to over 1,250 fewer total opioid prescriptions and 430 fewer high-dose opioid prescriptions dispensed annually among this sample of 72 clinicians, thus highlighting the sizeable impact of the AD program on modifying opioid prescribing behavior.

Findings from the restricted analyses reflect the AD program's impact if clinicians had been targeted to receive AD based on baseline opioid prescribing behavior. Most notably, only about half the number of clinicians in both groups prescribed a high-dose opioid in the pre-AD program period. Among the sample of 39 clinicians in the intention to change group, changes in the rates of high-dose opioid prescribing further decreased from 0.5 to almost 1 fewer high-dose opioid prescriptions dispensed on average per month compared to the sample of 33 clinicians in the no/low intention to change group. By excluding clinicians who did not prescribe high-dose opioids in the pre-AD program period in the restricted analysis, the effect of AD was magnified among the clinicians in the intention to change group. This finding provides support for the use of baseline behavior to identify clinicians who may reap the most benefit from targeted AD delivery. This approach may be most advantageous when the AD programs are resource-constrained and lacks the capacity for delivery to many clinicians.

In this study, the AD program incorporated recommendations from the CDC Guideline to improve education in a sample of primary care clinicians and motivate opioid prescribing behavior change. The findings from this study may be suggestive of increased willingness to uptake guidelines and higher motivation to change practice behavior among clinicians in the intention to change group relative to the no/low intention to change group. Clinical inertia, described as a poor willingness to uptake and translate evidence-based guidelines into clinical

practice,[148] may possibly explain the no/low intention to change practice responses from some clinicians. Several clinician-related factors may influence clinical inertia such as level of agreement with clinical guidelines, education, and motivation.[149] These factors may also be determinants of opioid prescribing behavior.[150] Future educational outreach programs focused on improving opioid prescribing behavior of clinicians should consider addressing these key factors to mitigate the impact of clinical inertia. Educational outreach programs may also consider incorporating motivational communication, an evidence-based behavior change approach drawn from motivational interviewing,[151] into detailer training sessions to further enrich their interactions with clinicians and to further facilitate the intended behavior change of the educational outreach program.

The findings from this study also support the need for further exploration of the correspondence between the use of standardized single-item intention to change measures and actual behavior change after AD programs. Use of single item or brief, psychometrically sound standardized measures can help to improve the quality of methods and measures used to evaluate the impact of AD programs, as well as assist in quality improvement and refinement of the AD delivery to clinicians. Self-reported intention to change practice behavior collected from clinicians immediately following the AD program may help to distinguish between frequent and infrequent prescribers prior to the implementation of an AD program. It may also provide an initial indicator of the AD program's impact on behavior change and help to identify clinicians that may warrant further educational outreach. Understanding clinicians' behavior prior to the AD program may add a richer context when interpreting self-reported responses to behavior change measures since many AD programs do not utilize baseline behavior to target their delivery. Collecting self-reported intention to change may also be useful in situations where those implementing AD programs are unable to measure actual behavior following the program due to resource limitations or lack of access to the relevant data for behavior change

measurement. Future AD programs that collect information on intentions to change behavior via self-report should evaluate its concordance with actual behavior.

Several limitations should be considered when interpreting the results of this research. Although a single-item was used as a proxy measure for actual behavior change in this study, concordance between self-report and actual opioid prescribing behavior was demonstrated in this particular context and should be replicated in other settings. Generalizability of our findings to other health systems may be limited since the clinicians included in this study were from a single large health system in the Chicago metropolitan area. Furthermore, the AD program was delivered to clinicians within a single health system regardless of prescribing patterns prior to the AD program, which is typical of AD programs. This lack of a targeted approach may have attenuated the observed effect of the AD program on clinicians' opioid prescribing behavior. Therefore, a restricted analysis was conducted including only clinicians with opioid prescribing data prior to the AD program. Since opioid prescribing data in the pre-AD program period were differentially higher between the intention to change and no/low intention to change groups, we cannot rule out regression to the mean as an explanation of our findings. This study was limited to two primary care specialties, thus impacting generalizability to other clinician specialties that prescribe opioids.

2.6 Conclusion

This study demonstrates alignment between self-reported intention to change practice behavior and actual behavior following an AD program focused on safe opioid prescribing. This research provides evidence to support self-reported intention to change practice behavior as a potential immediate indicator of actual change in opioid prescribing behavior following an AD program. Future educational outreach programs should consider targeted approaches and utilization of standardized intention to change measures when measuring actual practice behavior change, especially when resourced-constrained.

III. SECONDARY EFFECTS OF AN OPIOID-FOCUSED ACADEMIC DETAILING PROGRAM ON NON-OPIOID CONTROLLED SUBSTANCE PRESCRIBING IN PRIMARY CARE

3.1 Preface

This chapter addresses Aim 2 of the dissertation. It will be submitted for publication in a peer-reviewed journal as an article titled “Secondary Effects of an Opioid-Focused Academic Detailing Program on Non-Opioid Controlled Substance Prescribing in Primary Care”. The version for initial submission is presented here.

3.2 Introduction

Evidence-based approaches to educational outreach, particularly AD programs, are intended to improve medical decision-making.[8] AD uses specially trained personnel (i.e. detailers) to deliver current unbiased, evidence-based information via one-on-one, face-to-face visits with clinicians.[113] The CDC has endorsed AD as an evidence-based approach to combat the opioid crisis by supplementing clinicians knowledge on safe opioid prescribing.[112] Prior studies have evaluated the impact of AD among clinicians in primary care settings to modify opioid prescribing behavior and utilization of state PMPs that collect data on the dispensing of federally controlled substances.[122-125,145] These studies found AD was associated with improved opioid guideline adherence,[123,145] reduced high-dose opioid prescribing,[122] and increased PMP utilization.[124,125]

In 2016, the CDC released the *Guideline for Prescribing Opioids for Chronic Pain* in an effort to provide evidence-based guidance to clinicians on safe opioid prescribing practices.[21] AD programs that incorporate recommendations from the CDC Guideline may help clinicians learn to become more prudent about appropriate opioid prescribing. Key recommendations from the CDC Guideline include routinely reviewing information in state PMPs and avoiding concurrent prescribing of opioids and BZD. State PMPs can be used to assess high-risk patient

behavior such as receipt of high opioid dosages or concurrent use of opioids and BZD which is associated with an increased risk for opioid overdose.[130] As clinicians begin to use PMPs more consistently they may be more aware of a patient's history of prescription opioid and non-opioid controlled substance use.

Use of BZD and other select non-opioid controlled substances such as non-BZD sedative-hypnotics (i.e. eszopiclone, zaleplon, zolpidem, and zopiclone; the Z-drugs) and carisoprodol is associated with increased risks of abuse and overdose death.[131,132] BZD and non-BZD sedative-hypnotic utilization have increased in the past two decades due to more chronic use for anxiety and insomnia in spite of limited evidence to support their long-term use.[152] Increased abuse and misuse of carisoprodol have been noted reasons for its federally regulated classification as a schedule IV controlled substance.[129] Similar to carisoprodol, BZD and non-BZD sedative-hypnotics are also schedule IV controlled substances and are reported in state PMPs. Thus, AD programs focused on safe opioid prescribing that also include an educational component on PMP use may impact prescribing of both opioids and non-opioid controlled substances. The potential secondary effects of opioid-focused AD programs on prescribing of non-opioid controlled substances remain relatively unexplored despite the continued implementation of educational outreach programs to improve opioid prescribing among clinicians amidst the opioid crisis. Therefore, the objective of this study was to evaluate the secondary effects of an opioid-focused AD program on non-opioid controlled substance prescribing in primary care.

3.3 Methods

A quasi-experimental pre-post study was conducted to evaluate the impact of an opioid-focused AD program on prescribing of BZDs, non-BZD sedative-hypnotics, and carisoprodol in primary care. A D-I-D approach was used to compare changes in mean monthly BZD, non-BZD sedative-hypnotic, and carisoprodol prescribing. Primary care clinicians who received an opioid-

focused AD program were compared to a control group of primary care clinicians who did not receive the AD program. The AD program was delivered between June 2018 and August 2018. The D-I-D approach compared changes in prescribing from six months before the AD program (December 2017 to May 2018) to six months after the conclusion of AD program (September 2018 to February 2019) between both clinician groups. The Office for the Protection of Human Subjects at the University of Illinois at Chicago approved the study, and informed consent was obtained from all study participants who received the AD program. Clinicians were not compensated for study participation.

The AD program was implemented through a partnership with a large health system that provides primary care services throughout the Chicago metropolitan area and its surrounding suburbs [ref to main AD paper]. The program consisted of one-on-one, in-person visits between clinicians and academic detailers conducted at the health system's immediate care/walk-in clinics. The duration of AD visits averaged approximately 15 minutes. During each visit, the detailers discussed information related to safe opioid prescribing and tailored the interaction based on the needs of the clinician. The content of the visits included information on the CDC Guideline and tailored metrics on the clinician's past opioid prescribing. Six key messages from the CDC Guideline were selected as the focus of the detailing visits. These messages were: (1) Check the PMP for high opioid dosages and prescriptions from other clinicians, (2) Avoid concurrent BZD and opioid prescribing, (3) Use non-opioid treatments as first-line or routine therapy for chronic pain, (4) Start low and go slow when using opioids, (5) Incorporate strategies to mitigate risk factors for opioid-related harms, and (6) Offer treatment for opioid use disorder. As part of the visit, each clinician was provided with information on their individual opioid prescribing behavior as reflected in the PMP in the past six months that included: (1) average (i.e. mean) number of monthly PMP queries, (2) average number of monthly opioid prescriptions, (3) the number and percentage of total opioids prescribed categorized by daily

MME thresholds of <50 MME/day, 50-89 MME/day, and ≥90 MME/day, (4) average days supply/opioid prescription, (5) average daily MME/opioid prescription, and (6) average monthly number of patients co-prescribed opioids and BZDs.

Clinicians were eligible for an AD visit if they were licensed healthcare clinicians with opioid prescriptive authority (i.e. MD, DO, NP, and PA) who practiced in primary care, specifically family medicine or internal medicine. Resident physicians and pediatric specialties were excluded. We considered all clinicians who received at least one of two planned AD visits as exposed to the program (AD-exposed). To account for secular changes in opioid prescribing behavior, a control group of clinicians specialized in family medicine or internal medicine was identified from different large health systems providing primary care services in the Chicago metropolitan area. These control group clinicians did not receive AD visits over the course of the study period. Baseline characteristics of the clinicians receiving AD (i.e. sex, clinician specialty, clinician type, and years of practice) were collected during the AD visit. Baseline characteristics for each clinician in the control group were collected via publicly available information (e.g. health system websites). Clinician-level prescribing data for BZD, non-BZD sedative-hypnotics and carisoprodol were obtained from the IL PMP database.

The three outcomes measured in this study were mean monthly number of BZD, non-BZD sedative-hypnotics (i.e. eszopiclone, zaleplon, zolpidem, and zopiclone), and carisoprodol prescriptions, per clinician. These outcomes were measured during the pre-AD program period (December 2017 to May 2018) and compared with outcomes in the post-AD program period (September 2018 to February 2019) between the AD-exposed and control groups.

Characteristics of the AD-exposed and control groups were compared at baseline with the chi-square test for categorical variables and *t*-tests were used to compare differences in means for continuous variables. A D-I-D approach was used to compare pre-post changes in outcomes between the AD-exposed and control group.[147] Repeated measures linear regression

models were used with an unstructured covariance structure and a random effect for each clinician to account for correlation of outcomes within each clinician. Baseline characteristics were adjusted for in the model. The model included main effect terms for binary indicators of AD exposure (yes or no) and time (pre-AD program or post-AD program) and an interaction between the main effects. The β coefficient for the model interaction term represents the D-I-D estimate for the AD program's effect on the outcomes. More simply, the D-I-D estimate represented the pre-post difference in the prescribing outcomes between the AD-exposed group and the control group. For each outcome, a subgroup analysis was conducted where the population was restricted to clinicians who prescribed at least one non-opioid controlled substance in the pre-AD program period as the AD program would not be expected to impact clinicians who did not prescribe in the pre-AD program period. A 95% CI was presented for each β coefficient in the D-I-D analyses. A two-sided p-value < 0.05 was considered statistically significant. SAS version 9.4 (SAS Institute Inc.: NC, Cary) was used to perform statistical analyses.

3.4 Results

A total of 550 clinicians, 151 in the AD-exposed group and 399 in the control group, were included in the analysis **(Table VII)**. Clinicians were primarily physicians (90.4%), specialized in internal medicine (58.5%), and practiced for a mean of 20 years. Mean years of practice were higher in the control group compared to the AD-exposed group (21 vs. 18, $p < 0.01$). Compared to the control group, a higher proportion of AD-exposed clinicians were NP or PA (17.2% vs. 6.8%, $p < 0.01$) and specialized in family medicine (76.2% vs. 28.3% $p < 0.01$).

Table VII. Study 2 – Clinicians' Baseline Characteristics

Characteristics	**Overall**		**AD-exposed**		**Control**		***P***
Total Clinicians, n	550		151		399		
Sex, n (%)							
Female	286	(52.0%)	88	(58.3%)	198	(49.6%)	0.07
Male	264	(48.0%)	63	(41.7%)	201	(50.4%)	
Years of Practice, mean (SD)	20	(11)	18	(11)	21	(11)	<0.01
Clinician Type, n (%)							
MD	423	(76.9%)	87	(57.6%)	336	(84.2%)	<0.01
DO	74	(13.5%)	38	(25.2%)	36	(9.0%)	
NP	34	(6.2%)	18	(11.9%)	16	(4.0%)	
PA	19	(3.5%)	8	(5.3%)	11	(2.8%)	
Clinician Specialty, n (%)							
Family Medicine	228	(41.5%)	115	(76.2%)	113	(28.3%)	<0.01
Internal Medicine	322	(58.5%)	36	(23.8%)	286	(71.7%)	

Table VIII shows there were no pre-post differences in the mean monthly number of BZD prescriptions per clinician within the AD-exposed group (24.10 vs. 22.08, $p = 0.08$), however the mean monthly number of BZD prescriptions per clinician was significantly lower in the post-AD program period within the control group (21.94 vs. 19.19, $p < 0.01$). The pre-post mean monthly number of non-BZD sedative-hypnotic prescriptions per clinician within the AD-exposed group (8.39 vs. 8.25, $p = 0.75$) and within the control group (8.20 vs. 8.02, $p = 0.51$) were not significantly different. The mean monthly number of carisoprodol prescriptions per clinician were significantly lower in the post-AD program period within the AD-exposed group (0.32 vs. 0.22, $p < 0.01$) and within the control group (0.27 vs. 0.23, $p = 0.04$).

Table VIII. Summary of Pre-Post AD Program Mean Monthly Prescribing Statistics and Difference-in Differences (D-I-D) Results for AD-exposed vs. Control

	AD-exposed			Control						
	Pre	**Post**	**Δ**	**Pre**	**Post**	**Δ**	**D-I-D**	**(95% CI)**	**D-I-D restricted subgroups**	**(95% CI)**
BZD prescriptions	24.10	22.08	-2.02	21.94	19.19	-2.75*	0.73*	(0.14, 1.31)	1.10*	(0.44, 1.75)
Non-BZD sedative-hypnotic prescriptions	8.39	8.25	-0.14	8.20	8.02	-0.18	0.04	(-0.22, 0.31)	0.08	(-0.24, 0.41)
Carisoprodol prescriptions	0.32	0.22	-0.10*	0.27	0.23	-0.04	-0.06*	(-0.11, -0.01)	-0.21*	(-0.34, -0.06)
***** *p*-value < 0.05										
Δ **=** represents the pre-post difference in the prescribing outcomes between the AD-exposed group and the control group										
D-I-D = represents the pre-post difference in the prescribing outcomes between the AD-exposed group and the control group										
D-I-D restricted subgroups = represents the pre-post difference in the prescribing outcomes between the AD-exposed group and the control group among clinicians with non-opioid controlled substance prescribing data in the pre-AD program period										

Although the mean monthly number of BZD prescriptions decreased in both groups after the AD program, in the main D-I-D analyses BZD prescribing in the AD-exposed group declined at a slower rate following the AD program. The difference in the declining rate of mean monthly BZD prescriptions was higher by 0.73 (95% CI: 0.14, 1.31) in the AD-exposed group compared to the control group following the AD program **(Table VIII).** There was no significant change (0.04 [95% CI: -0.22, 0.31]) in the pre-post mean monthly rate of non-BZD sedative-hypnotic prescriptions between the AD-exposed and control groups following the AD program. Although infrequently prescribed in both groups before and after the AD program, the rate of mean monthly carisoprodol prescriptions was marginally lower by 0.06 (95% CI: -0.11, -0.01) in the AD-exposed group compared to the control group following the AD program.

When restricting the D-I-D analyses to clinicians who prescribed at least one BZD prescription in the pre-AD program period, the mean monthly number of BZD prescriptions in the AD-exposed group declined at a slower rate following the AD program. The difference in the declining rate of mean monthly BZD prescriptions was higher by 1.10 (95% CI: 0. 44, 1.75) in the AD-exposed group (N = 143) compared to the control group (N = 334) following the AD program. Among clinicians who prescribed at least one non-BZD sedative-hypnotic prescription in the pre-AD program period, there was a no significant change (0.08 [95% CI: -0.24, 0.41]) in the pre-post mean monthly rate of non-BZD sedative-hypnotic prescriptions between the AD-exposed (N = 135) and control groups (N = 307). Lastly, among clinicians who prescribed at least one carisoprodol prescription in the pre-AD program period, the rate of mean monthly carisoprodol prescriptions was marginally lower by 0.21 (95% CI: -0.34, -0.06) in the AD-exposed group (N = 50) compared to the control group (N = 124) following the AD program.

3.5 Discussion

This study explored the extent to which an opioid-focused AD program with a PMP educational component had secondary effects on non-opioid controlled substance prescribing in

primary care. The mean monthly number of BZD prescriptions was lower in both the AD-exposed and control groups in the period after the AD program was administered, but there was more decline in the control group by almost one BZD prescription per month per clinician. There were no meaningful changes in non-BZD sedative-hypnotic between the AD-exposed and control groups. A statistical difference, though not considered to be clinically meaningful, was found between the two groups in carisoprodol prescribing. These results were consistent when restricting to only those clinicians who prescribed at least one non-opioid controlled substance in the pre-AD program period. The findings of the study suggest that opioid-focused AD programs may have secondary effects on prescribing of non-opioid controlled substances outside of opioids.

The change in BZD prescribing after the AD program in the AD-exposed group compared to the control group were unexpected. The rate of BZD prescribing was higher by nearly one prescription per month in the AD-exposed group relative to the control group following the AD program. While this higher rate may seem inconsequential on the individual clinician level, based on the range of the 95% CI as few as 250 to more than 2,300 additional BZD prescriptions would be dispensed annually among this sample of 151 clinicians. Interestingly, a concurrent study found a 0.84 (95% CI: -1.35, -0.32) reduction in the rate of total opioid prescriptions dispensed per month per clinician in the AD-exposed group compared to the control group after the AD program [ref to main AD paper]. The contrasting relative changes in the rates of opioid and BZD prescribing after the AD program among the AD-exposed group compared to the control group may be suggestive of a compensatory shift to BZD prescribing triggered by opioid-focused AD programs.

Growing evidence has continued to emerge on the lack of significant benefit opioids provide in managing chronic and musculoskeletal pain conditions relative to non-opioids like non-steroidal anti-inflammatory drugs and acetaminophen.[30,153] Due to the increased awareness

of the harms associated with opioids, clinicians may divert their prescribing to drug classes with a similar lack of benefit and potential harms of their own, such as BZD.[154] This notion may be supported by recent data on disparate national prescribing trends which highlighted increased BZD use for musculoskeletal pain conditions and declining opioid use.[155,156] These trends in prescribing may be suggestive of a shift from problematic opioid prescribing towards problematic BZD prescribing. The higher relative rate in BZD prescribing among the AD-exposed group compared to the control group following the AD program may be suggestive of a potential shift towards BZD as the prescribing of opioids for pain management continues to wane among clinicians. Our findings suggest opioid-focused AD programs should be cognizant of this potential unintended secondary effect on prescribing of non-opioid controlled substances like BZD. Consideration of this unanticipated effect on BZD prescribing is warranted prior to large scale implementation of AD programs on safe opioid prescribing.

Our findings may also support the growing calls to action to address overuse and overprescribing of BZD.[157] Opioid-focused AD programs can be leveraged as an opportunity to intervene on both opioids and BZD prescribing. Education on evidence-based guidelines for BZD prescribing, risks of BZD use and alternative pain management options may be important components to integrate into opioid-focused AD programs to help address inappropriate prescribing of BZD. Additionally, incorporation of clear, actionable guidance on how to use the data found in state PMPs into opioid-focused AD programs may help to facilitate informed clinical decision-making. State PMPs may also consider the development and integration of guideline-concordant recommendations for safe opioid and BZD prescribing directly into their databases.[21] These recommendations may help to facilitate clinicians' decision-making when reviewing the history of a patient's controlled substance use to determine the medical necessity and appropriateness of opioid or non-opioid controlled substance prescriptions.

These results should be interpreted in the context of several limitations. AD-exposed

clinicians received the program whether they prescribed controlled substances in the pre-AD program period or not. By including clinicians who did not prescribe controlled substances in the pre-AD program period, the impact of the AD program on prescribing of non-opioid controlled substances may have been attenuated. To account for this, we conducted subgroup analyses including only those clinicians who prescribed at least one non-opioid controlled substance in the pre-AD program period. The findings from our study may not be generalizable to other health systems in other geographical areas in the US since the clinicians used for this study were from large health systems in the Chicago metropolitan area. While the control group clinicians were selected based on primary care specialty and geographic location, selection bias may have been present due to the differences in baseline characteristics between the two primary care groups. Although baseline characteristics were dissimilar between the two groups, the impact of the baseline characteristics on prescribing outcomes was not expected to be differential between the pre and post-AD program periods due to their immutable and time-invariant nature. Unmeasured differences between the AD-exposed group and control group may have affected the impact of the opioid-focused AD program on non-opioid controlled substance prescribing. Lastly, this study was limited to selected primary care specialties of family medicine and internal medicine, thus impacting generalizability to other clinician specialties.

3.6 Conclusion

A concerning secondary effect of an opioid-focused AD program may be a compensatory shift towards higher BZD prescribing as clinicians become more careful regarding opioid prescribing. Our findings may suggest the need for incorporation of targeted education on appropriate BZD prescribing into opioid-focused AD programs as a featured component. Further investigation of these findings is warranted prior to widespread implementation of opioid-focused educational outreach programs.

IV. IDENTIFICATION OF BARRIERS TO SAFE OPIOID PRESCRIBING IN PRIMARY CARE THROUGH ACADEMIC DETAILING

4.1 Preface

This chapter addresses Aim 3 of the dissertation. It has been submitted for publication at a peer-reviewed journal as an article titled “Identification of Barriers to Safe Opioid Prescribing in Primary Care through Academic Detailing”. The initially submitted version is presented here.

4.2 Introduction

The opioid epidemic in the US has become a major health crisis with President Donald Trump declaring opioids a “public health emergency” on October 26, 2017.[1] Over 47,000 opioid-related overdose deaths occurred in the US in 2017, of which about 35% involved a prescription opioid.[2] Compared to other specialties, primary care practitioners (e.g. family medicine and internal medicine) comprise approximately 50% of controlled substance prescribers and account for the majority of dispensed opioid prescriptions. [3,4,158] PCPs have reported feeling uncomfortable prescribing opioids and have expressed concern regarding opioid misuse, abuse, and addiction. [5] Moreover, limited pain management training provided in US health professional schools and during postgraduate training[159] has also contributed to the lack of confidence PCPs express in their ability to manage patients with chronic pain.[6,7] Targeted education, such as AD, is a means of modifying and improving opioid prescribing behavior.

Academic detailing is an educational outreach strategy designed to improve prescribing and other medical decisions by increasing awareness and use of evidence-based practices.[8] AD uses specially trained personnel (i.e., detailers) to provide healthcare practitioners with current unbiased, evidence-based information through individual, face-to-face visits. [113] Studies using AD to modify prescribing behavior related to opioids have found associations with modest reductions in prescription opioid-related mortality[121] and high-dose opioid prescribing[122]. Additionally, AD studies have found substantive improvements in adherence to opioid guidelines

[123] and PMP use [124,125].

The AD visit represents not just an opportunity to share evidence-based practices; in addition, it can be leveraged as a tool to gather information from providers. While previous AD studies have focused on the impact of direct educational outreach visits to improve prescribing activities related to opioids,[121-125,145,160,161] there was a limited focus on the structure and processes of care that present as barriers to implementing change in opioid prescribing behavior. Understanding these barriers can help to inform new strategies and reinforce existing ones intended to facilitate safe opioid prescribing practices. Prior research conducted on small samples within the VHA, examined barriers to safe opioid prescribing in primary care.[133,134,162] To build on the existing literature, the objective of this study was to identify barriers to safe opioid prescribing among PCPs through an opioid-focused AD program.

4.3 Methods

This was a cross-sectional analysis of qualitative data collected as part of an AD program focused on safe opioid prescribing in primary care. The institutional review board at the UIC approved this study, and informed consent was obtained from all participants. No compensation was provided to participants for their involvement in the study. The AD program was developed and implemented through a partnership with an independent health system in Illinois, serving residents in Chicago and its surrounding suburbs.

Health system leadership (i.e. CMO and Medical Director of Pain Management) supported the delivery of the AD program to their providers and encouraged voluntary participation through a system-wide email describing the initiative. The health system provided a list of PCPs (n=226) which contained names of providers and clinic managers, provider specialties, and clinic locations and contact information to facilitate the delivery of the AD program. Research staff attempted to schedule a 15 to 30-minute appointment with providers through the clinic managers. Up to two contact attempts were made to schedule visits. If

providers agreed to participate, a visit was scheduled. Detailers presented to clinic locations for their scheduled appointments and met with the providers, one-on-one, in a private location where they presented the study and obtained their written informed consent.

The AD program was delivered from June 2018 to August 2018. Licensed healthcare practitioners with prescriptive authority (physicians i.e., MD and DO, NP, and PA) who specialized in primary care (limited to family medicine or internal medicine including geriatric medicine) were eligible to participate (N=226). Visits were conducted at the health system's immediate care/walk-in clinics throughout the Chicago metropolitan area during regular office hours. Visits included the following components: 1) a review of six key messages from the CDC Guideline for Prescribing Opioids for Chronic Pain [21]; 2) provision of individualized provider-specific information on past opioid prescribing behavior obtained from the IL PMP; 3) administration of a measure to assess provider satisfaction with the AD program; and 4) additional resources to facilitate safe opioid prescribing practices.

Specially trained detailers consisted of eight first- and second-year Doctor of Pharmacy (PharmD) students and two licensed pharmacists from the UIC College of Pharmacy. The detailers received standardized AD training from study team members who had completed formal training from the National Resource Center for Academic Detailing (NaRCAD).[163] The training occurred over two days and included presentations on AD, the visit components, logistics (e.g. scheduling of AD visits, travel to clinic sites, and reimbursement), and simulated visits. Each detailer's ability to deliver the AD was assessed during the simulation where direct feedback was provided by the trained study personnel.

Following each AD visit, detailers entered field notes into a secure, Internet-based application. Detailers were instructed to describe all aspects of each encounter including questions and concerns expressed by providers. Thematic analysis was used to identify themes described within the field notes related to opioid prescribing barriers in primary care. This

analytic method was used because of its ability to summarize large amounts of data to allow for a rich and detailed account of the data collected.[164,165] Subthemes were represented as a statement or phrase that captured something important about the data in relation to the research objective. Themes were generated in an inductive, qualitative approach and represented some level of recurring, patterned response or meaning within the data. Provider characteristics were removed from the field notes prior to analyzing the data to mitigate bias. The process used to conduct the thematic analysis involved the following iterative steps.

Analytic reviewers consisted of a clinical psychologist with qualitative research experience, a pharmacist and PhD student, and a research assistant. Reviewers met initially to become familiar with the data and discuss the coding scheme. An initial list of codes and definitions was developed by the three reviewers over two meetings. Additional codes were added as coding proceeded. The three reviewers independently coded the first 10 sets of field notes to identify and systematize the concepts and categories into subthemes. After initial coding, reviewers met to compare codes and refine definitions. This process was repeated on the next 10 field notes. After meeting again to compare codes, no discrepancies were noted. Two reviewers independently coded the remaining field notes. Subsequently, the three reviewers met to compare codes with the principal qualitative reviewer leading discussion to resolve remaining discrepancies. A final meeting focused on organizing the codes into larger themes where six overarching themes related to opioid prescribing barriers were identified.

4.4 Results

AD visits were conducted with 186 of 226 identified providers who agreed to participate (82% participation rate). The majority of providers who participated were female (55%, n = 103), allopathic physicians (52%, n = 96), and specialized in family medicine (80%, n = 149) (**Table IX**). Median AD visit length was 15 minutes and ranged from 5 to 25 minutes (**Table IX**). The median years of practice for providers were 12 years. Barriers to opioid prescribing were

organized into six themes: 1) gaps in knowledge; 2) lack of PMP utilization; 3) patient pressures to prescribe opioids; 4) insurance coverage policies; 5) provider beliefs; and 6) health system pain management practices. The themes are described below with representative descriptions and in decreasing frequencies of themes identified.

Table IX. Study 3 – Clinicians' Baseline Characteristics

Characteristic	Total (N=186)
Sex, n (%)	
Female	103 (55%)
Male	83 (45%)
Provider Type, n (%)	
MD	96 (52%)
DO	64 (34%)
NP	18 (10%)
PA	8 (4%)
Provider Specialty, n (%)	
Family Medicine	149 (80%)
Internal Medicine	37 (20%)
Years of Practice	
Median	12
Interquartile Range	3 - 23
AD Visit Length (minutes)	
Median	15
Interquartile Range	12 - 15

One hundred and twenty-two field notes identified six barriers coded as gaps in knowledge. Two barriers in this theme related to naloxone. Providers indicated a gap in knowledge regarding patient access to and affordability of naloxone and administration techniques for commercially available naloxone formulations (i.e. intranasal vs. intramuscular). Three additional barriers in this theme related to opioid and non-opioid treatments. Providers expressed a lack of knowledge about particular drugs qualifying as prescription opioids (e.g. acetaminophen with codeine, tramadol, etc.) and an inability to calculate morphine milligram equivalents (MME), a conversion factor for standardization and comparison of opioid doses. Further, providers expressed uncertainty about safe non-opioid treatments to prescribe for patients with pain and common comorbidities (e.g. hepatic or renal insufficiency). The final

barrier in this theme was lack of provider awareness of their personal opioid prescribing habits prior to initially being presented with individualized opioid prescribing data during AD visits.

Sixty-seven field notes identified four barriers coded as lack of PMP utilization. Three of the barriers in this theme related to the PMP website. Providers indicated they had difficulty registering for the PMP, problems logging in after successful registration, and difficulty navigating the PMP website. The final barrier in this theme related to the time required to look up patients, which ultimately led to a lack of use of the PMP. Collectively, these logistical PMP utilization factors hindered providers from consistently using the state PMP.

Nineteen field notes identified patient pressures as a barrier believed to impact safe opioid prescribing. For example, PCP participants expressed feeling pressured to renew opioid prescriptions among patients from other PCPs who previously managed them with opioids. Patient demands for opioids complicated providers' ability to assess the actual need for opioids. Thus, a few providers were concerned about the impact of having dissatisfied patients in the health system. Additionally, mid-level providers (e.g. nurse practitioner or physician assistant) expressed challenges when attempting to discontinue concurrent opioid and BZD prescriptions to patients regularly receiving them from other PCPs.

Twelve field notes identified two insurance coverage-related barriers. First, providers indicated coverage policies (e.g. prior authorizations) limited access to and affordability of prescribed non-opioid treatments (e.g. lidocaine patches, diclofenac gel, and acupuncture). Providers reported that insurance coverage policies affected their ability to keep patients opioid-naïve when prescription opioids were more accessible and less costly compared to some non-opioid treatments. Second, providers reported utilization management policies (e.g. visit limits) curtailed some patients from visiting pain specialists at internal outpatient pain management clinics within the health system. As a result, PCPs expressed frustration about insurance coverage limiting their ability to refer certain patients who required more specialized pain

management.

Nine field notes identified two barriers related to provider beliefs. The first barrier was providers simply not believing that their personal practice was impacted or at risk for being impacted by opioid dependence. They recognized that there was an opioid epidemic nationally; however, they felt that their patients were not involved or at risk. The second barrier in this theme was providers' experiences with personal tragedy due to the opioid epidemic, such as the loss of a family member from an opioid overdose. As a result, some providers admitted to rarely prescribing opioids and often referred patients to outpatient pain clinics whenever possible.

Five field notes identified three barriers related to health system pain management practices. First, providers reported ambiguity regarding pain management policies about the clinical use of tramadol. Second, providers indicated time constraints to perform a full pain assessment of each patient during routine encounters as an impactful system-wide issue. Lastly, some providers expressed disagreement with the MAT practices (e.g. use of methadone) at internal outpatient pain management clinics for the treatment of mutual patients with opioid use disorder due to personal experiences with patients unable to be tapered off of MAT once initiated.

4.5 Discussion

In order to identify important targets for programs, it is necessary to understand the challenges providers experience when considering the use of opioids in the management of patients with pain. An AD program targeted to PCPs was leveraged to identify barriers related to safe prescribing of opioids. Coding of field notes obtained through open-ended feedback from 186 AD visits with PCPs resulted in the identification of six themes related to barriers impacting safe opioid prescribing in primary care. Gaps in knowledge and lack of PMP utilization were most commonly identified. Additional, albeit less commonly identified, issues raised by providers included pressure from patients to prescribe opioids, limited patient access to other pain

treatments/specialists due to insurance coverage, provider beliefs, and health system pain management practices. Overall, the findings from this study underscore issues relevant to safe opioid prescribing and pain management practices to improve patient outcomes.

To our knowledge, the current study is the largest qualitative study focused on the identification of barriers to safe opioid prescribing in primary care and the first to describe barriers among PCPs practicing outside of the VHA. The results were largely consistent with those reported among PCPs within the VHA including knowledge gaps, provider attitudes and beliefs, patient-provider interactions, and health system pain management practices [133,134,162]. Novel findings highlighted the impact of insurance policies on opioid prescribing due to limited reimbursement for alternative pain management and the PMP as barriers to safe opioid prescribing in primary care. This study also demonstrated that field notes associated with an AD visit can be used as a novel approach to identify and facilitate barriers to safe opioid prescribing among PCPs within a health system on a large scale.

Gaps in knowledge were the most commonly identified barriers to safe opioid prescribing. This finding is not surprising given the limited amount of courses incorporating pain management in US health professional schools.[159] Due to the evolving pain management landscape, there is a clear need for increased pain management education.[166] Direct educational outreach through AD is an increasingly used strategy to supplement providers' knowledge with the most current, evidence-based information related to pain management and safe opioid prescribing. Development of an AD program can be tailored to include relevant resources and materials to facilitate safe opioid prescribing that are applicable to the targeted setting (e.g. primary care). However, implementation on a large-scale in the targeted setting may be challenging due to factors that may impact provider engagement such as time constraints and uncertainty about the value of AD. Thus, incorporating useful incentives into the AD program may overcome challenges to provider engagement and large-scale AD

program implementation within a health system. A potential incentive may be to provide continuing medical education (CME) credit related to opioid prescribing through an AD program accredited to provide CME. The AD program can include resources to enhance provider communication skills with patients as a component of the CME since providers have increasingly expressed a desire to better maintain provider-patient relationships while practicing safe opioid prescribing behavior. [167] Expanding opportunities for providers to gain opioid-related CME credit is especially relevant due to growing the state legislative requirements for licensed controlled substance prescribers in order to maintain their licensure.[168]

Barriers to PMP utilization were the second-most frequently reported theme. PMPs are statewide electronic databases that collect timely information from retail pharmacies on dispensing of schedule II through V controlled substance prescriptions (e.g. drug name, payment type, prescriber information, etc.).[92] Thus, PMPs can be used to identify problematic controlled substance utilization behaviors and support clinical decision-making to reduce prescription opioid misuse, abuse, and diversion.[93] Effectiveness of PMPs relies on prescribers to access and review the database prior to prescribing controlled substances but prescribers have reported a lack of routine use even though many are aware of the PMP and its utility.[96,97] Moreover, a lack of clear guidance on how to proceed with the information found in PMPs can also pose a barrier to PMP utilization by providers. The identified barriers were consistent with common barriers to PMP utilization described in previous studies which included online registration and access difficulties, lack of time to access PMPs, and lack of PMP usability.[98,99] Recommended strategies to overcome these barriers include mandatory PMP registration to facilitate increased utilization, integration of PMPs with electronic medical records to improve direct PMP access, and consent for authorized delegates to access the PMP on the provider's behalf to reduce time constraints on providers.[99-101,169] Implementation of these recommended strategies has been associated with modest reductions unsafe opioid prescribing and

prescription opioid overdose deaths which suggest PMPs can be helpful, although, insufficient on their own.[102-104] However, the PMP is the main tool providers have at their disposal to assess a patient's controlled substance history. Therefore, the development of user-centered online training programs by state PMPs can help to improve utilization and navigation of the PMP database. [170] Aligning such training programs with evidence-based guidelines may facilitate more effective use of the PMP and enhance clinical decision making.

Less frequently reported, although critically important, were insurance-related barriers which impacted access to, and affordability of, pain treatments and specialists. Providers reported that patients' insurance often lacked coverage for non-opioid treatments. This left providers with few options outside of prescription opioids which were more often covered. While non-opioid treatments are recommended as initial pain management options by evidence-based guidelines for chronic pain, [21,171] coverage policies are inconsistent and were noted as factors impeding access to and affordability of non-opioid treatments relative to prescription opioids. [89,90] Adoption of coverage policies aligned with evidence-based guidelines, such as step therapy requirements with non-opioid treatments prior to opioid initiation, would incentivize initial use of non-opioid treatments. Implementation of such policies could broaden the selection of non-opioid treatments to make guidelines easier to follow which may help to reduce prescription opioid misuse, abuse, and overdose death. [89,91] Moreover, providers expressed a desire to refer patients for specialized pain management, but those efforts were hindered by utilization management policies. Affordability of visits to pain specialists may be increasingly challenging for patients when insurance coverage is limited. By revising current coverage and reimbursement policies to reflect evidence-based guidelines which support increased access to non-opioid treatments and pain management services,[172] insurers can play a pivotal role in facilitating safe opioid prescribing practices in primary care.

Although AD has typically aimed to modify prescribing behavior at the provider-level,

collecting information from providers during the AD visit and sharing it with health system leadership may provide an opportunity for system-wide improvements. With challenges to implementing the CDC guideline in practice becoming more prominent, [172] AD may be used as an opportunity to clarify evidence-based recommendations with providers to ensure their appropriate application. However, solutions to address insurance-related barriers require action at the health plan/insurer level which influence guideline concordant opioid prescribing practices.

The results must be interpreted in consideration of several limitations. Providers were not asked directly about barriers they perceived to opioid prescribing using standardized questions. Data were comprised of field notes composed immediately following visits. Although providers were not directly asked about barriers to opioid prescribing, themes were generated from open-ended questions and feedback. Detailers were asked to provide information on all aspects of the visit; however, there was much variation in the length and detail of the field notes for each documented visit. The AD program was delivered to providers regardless of their prior opioid prescribing patterns which may have impacted the barriers identified. Providers specializing in pediatrics and obstetrics/gynecology were not included among the PCP participants, which may have impacted the barriers identified. Participating providers specialized in primary care and practiced within a single health system in the Chicagoland region, potentially limiting the generalizability of our findings. However, this subgroup of providers prescribes the largest proportion of opioids, and therefore, the findings remain relevant.

4.6 Conclusion

Six themes were identified related to barriers impacting safe opioid prescribing among a large group of PCPs through AD. These findings can be used to inform targeted efforts to facilitate improved clinical decision-making related to opioid prescribing and pain management. Gaps in knowledge and lack of PMP utilization were most frequently identified. These findings

support the need for enhanced pain management education and continued efforts to maximize PMP utilization to facilitate safe opioid prescribing in primary care. Additionally, our findings suggest a need for adoption of evidence-based coverage and utilization management policies by insurers that increase access to and affordability of non-opioid treatments and pain management services. This study also highlights the use of AD as an approach to identify barriers to safe opioid prescribing and facilitate solutions to the identified barriers.

V. CONCLUSION

Since 1999, more than 200,000 prescription opioid-related overdose deaths have occurred,[32] with over 17,000 occurring in 2017 alone.[2] Primary care clinicians account for nearly half of the opioids dispensed in the US and have reported inadequate education related to opioids.[4] This has impacted their ability to safely and appropriately manage chronic pain.[4,6] Targeted education delivered through AD can effectively modify and improve prescribing behavior. As the opioid crisis continues to be a prevalent issue in the US, investigation of strategies used to modify prescribing behavior, such as educational outreach, is warranted. This dissertation is comprised of three studies that examined the impact of an opioid-focused AD program on controlled substance prescribing and identification of barriers that may preclude safe opioid prescribing in primary care. This work adds to the body of evidence to support AD as an effective strategy to modify opioid prescribing behavior in primary care.

In the first study, clinicians' self-reported practice change intentions were compared with opioid prescribing behavior following the AD program. Clinicians in the intention to change group had a 1.48 (95% CI: -2.48, -0.47) reduction in the mean monthly rate of total opioid prescriptions and a 0.50 (95% CI: -0.69, -0.31) reduction in the mean monthly rate of high-dose opioid prescriptions compared to clinicians in the no/low intention to change group. Among clinicians with baseline high-dose prescriptions, high dose-opioid prescriptions were further reduced from 0.50 to nearly 1 fewer prescription per month among clinicians who reported an intention to change relative to clinicians who reported no/low intention to change.

This study included elements from both process and program evaluation. The process of the AD program was evaluated via the provider satisfaction survey which was administered to clinicians immediately after each AD visit. The survey included a single-item practice change measure that could be used as part of a quality assurance tool when evaluating the detailers' delivery of the educational material. If a detailer is consistently associated with low or no

likelihood of change it may be important to determine how that detailer is different from other detailers.

More importantly, this item could be used as an indicator of a response to the AD visit. It is possible for programs to use this measure to understand the potential effects of the AD visits. In order for this to be useful as an intermediate marker of change in behavior, it was necessary to compare practice change intentions with changes in opioid prescribing. Specifically, the concordance of clinicians' self-reported practice change intentions was compared with their actual behavior. Clinicians' self-reported intentions and actual opioid prescribing behavior were found to align following the AD program. Based on these findings, future AD programs may consider the use of a standardized single-item intention to change measures to provide an immediate indicator of actual behavior change following the program. Such a measure could help to provide an initial indicator of the AD program's impact on behavior change. A single-item intention to change measures may be an advantageous consideration for AD programs for several reasons. First, if they are unable to measure actual behavior after the program this measure could be an indicator of the effectiveness of the program. Second, when targeting clinicians based on past high-dose opioid prescribing behavior, reductions in high-dose opioid prescribing were magnified among clinicians in the intention to change group compared to the no/low intention to change group. Therefore, using baseline prescribing behavior to identify clinicians may help to guide delivery of the AD program to clinicians who may benefit the most from educational outreach. Targeted approaches may be most desired by AD programs with modest-funding and limited ability to visit with a large number of clinicians.

In this study, baseline prescribing behavior was differential between the intention to change group and the no/low intention to change group and therefore may have reduced the internal validity of this study. Evaluating changes in prescribing among clinicians with similar baseline prescribing behavior may have helped to improve the internal validity of this study and

mitigated the concern for regression to the mean as an explanatory factor for the findings. The findings from this study may not be generalizable to clinicians practicing in rural settings, not in primary care due to known variations in opioid prescribing due to geography[156] and clinician specialty[4].

In the second study, BZD prescribing in the AD-exposed group and control group declined after the AD program but the difference in the declining rate was higher by 0.73 (95% CI: 0.14, 1.31) in the AD-exposed group relative to the control group. Interestingly, opioid prescribing among this sample of AD-exposed clinicians significantly declined at a similar rate (-0.84, 95% CI: -1.35, -0.32) after the AD program compared to the same control group. These findings may be suggestive of a compensatory shift to BZD prescribing prompted by the opioid-focused AD program. This unintended and unexpected impact of the AD program on BZD prescribing warrants further consideration and investigation prior to the large-scale implementation of opioid-focused educational outreach programs. Additionally, the differential clinician characteristics between the AD-exposed group and control group and inclusion of providers with no history of non-opioid baseline prescribing history may have impacted the internal validity of this study. However, this concern was accounted for analytically in subgroup analyses. The findings of this study may not be generalizable to clinicians outside of primary care or clinicians in rural areas which may be an area for further research.

These findings highlight there may be a potential need for future opioid-focused AD programs to feature education on safe and appropriate BZD prescribing. Future programs may also consider including information on misuse and abuse of non-opioid controlled substances such as gabapentin. Concurrent use of gabapentin and opioids is associated with an increased risk of opioid-related death.[173] This added educational component may help provide clinicians with a more comprehensive overview of dangerous drug combinations that increase the risk for opioid overdose. While adding content to AD visits may be warranted, the pragmatic

implications have to be considered. Specifically, is it feasible to expand the number of key messages within a program given the time constraints of an AD visit (e.g. 15-30 minutes). Therefore, future AD programs will need to prioritize the importance of key messages delivered to clinicians in order to facilitate the intended behavior modification.

In the third study, documented feedback of each initial visit with clinicians during the AD program was leveraged to identify barriers to safe opioid prescribing in primary care. There were six commonly reported barriers which included: inadequate pain management knowledge, lack of routine PMP use, pressure from patients to prescribe opioids, insurance coverage policies for non-opioid treatments to manage chronic pain, attitudes and beliefs around opioid prescribing, and internal health system pain management policies and practices. The identified barriers support the need for continued efforts to enhance pain management education for clinicians, maximize PMP utilization/usability, and increase access to, and affordability of, non-opioid treatments for chronic pain. These findings are likely generalizable to primary care clinicians in urban areas, however, barriers to safe opioid prescribing in primary care among clinicians in rural settings remain underexplored and is an area for further research.

The findings from this study demonstrate how AD can be leveraged to maximize the interaction with clinicians to uncover barriers that may preclude appropriate prescribing. Future opioid-focused AD programs should consider incorporating strategies to address the barriers clinicians reported in this study to better facilitate safe opioid prescribing. System-level barriers, such as lack of PMP use, can be addressed by integrating PMPs into electronic health records. PMP-related barriers were overcome through our direct relationship with the IL PMP. AD programs should consider establishing important partnerships with relevant stakeholders (e.g. state PMPs) prior to AD program implementation to facilitate overcoming barriers clinicians may encounter. Additionally, opioid-focused AD programs should consider including education and training on MAT to enhance clinicians' ability to directly manage patients with OUD. The

feedback of this information to health systems can be an important part of an AD program so that action can be taken on the identified barriers.

The results from these three studies were based on the conceptual framework adapted from the COM-B system **(FIGURE I)**. The COM-B system included components of capability (C), opportunity (O), motivation (M), and their influence on behavior (B) change. Capability is the individual's capacity to participate in the corresponding activity, opportunity represents barriers that may preclude the behavior change, and motivation represents processes that direct behavior.[135] The conceptual framework for this dissertation **(FIGURE II)** was adapted to include an additional component for unintended behavior. The added unintended behavior component reflects the hypothesized downstream relationship between intended behavior change (i.e. reductions in opioid prescribing in the AD-exposed group relative to a control group) and unintended behavior change (i.e. reductions in BZD, non-BZD sedative-hypnotic, and carisoprodol in non-opioid prescribing in the AD-exposed group relative to a control group). The rationale for this added component was due to the evaluation of secondary effects of the opioid-focused AD program on the prescribing of other non-opioid controlled substances.

In the first study, practice change intentions were hypothesized to align with changes in prescribing of total opioids and high-dose opioids after the AD program. The findings from this study are in line with the conceptual framework and suggest the AD program may have improved the capability to safely and appropriately prescribe opioids among clinicians in the intention to change relative to the no/low intention to change group. In the second study, the impact of the AD program on opioid prescribing was hypothesized to "spillover" and influence non-opioid controlled substance prescribing in the AD-exposed group compared to a control group. Although reductions in opioid prescribing were found in the AD-exposed group compared to the control group after the AD program, there were no substantive or clinically meaningful changes in non-BZD sedative-hypnotic and carisoprodol prescribing between the two groups.

Interestingly, BZD prescribing declined in both groups following the AD program, however, at a slower rate in the AD-exposed group compared to the control group. While these findings were counter to what was hypothesized in the conceptual framework, they may be helpful to inform future opioid-focused AD programs of their potential unintended consequences on controlled substance prescribing outside of opioids. Lastly, the third study leveraged the opioid-focused AD program to identify several barriers that impact clinicians' opportunity to safely and appropriately prescribe opioids. Heightened awareness of the identified barriers can inform areas of need that future opioid-focused AD programs can address to better facilitate clinicians' ability to overcome obstacles related to safe and appropriate opioid prescribing in primary care.

The research undertaken in this dissertation is both exploratory and confirmatory. Specifically, the first two studies were exploratory and will require replication prior to widespread uptake by future opioid-focused AD programs and policymakers. The third study of this dissertation is confirmatory and largely consistent with prior literature on barriers to safe opioid prescribing in primary care. These studies have added to the limited body of AD literature and provide support for continued AD efforts to improve opioid prescribing behavior. The current evidence for AD could be further strengthened by exploring the research objectives from this dissertation among primary care practitioners in rural settings.

The findings from this dissertation will have several public health implications. First, these findings have been used to help support statewide policy decisions such as the signing of House Bill 3097 (305 ILCS 5/12-4.52) by Illinois Governor JB Pritzker on August 9th, 2019. This legislation requires the Department of Human Services to develop and implement educational outreach programs to provide prescribing clinicians with evidence-based information on opioids and pain management, in addition to other relevant topics involving pharmaceuticals. Second, the findings from this research have been influential in obtaining additional funding to further evaluate AD as an effective strategy for opioid overdose prevention across the state of Illinois.

Overall, the actions taken by state legislators and national agencies will facilitate subsequent opioid-focused AD program delivery to clinicians statewide. These efforts will help to improve safer prescribing of opioids and potentially reduce opioid-related mortality in Illinois.

This dissertation provides evidence-based and practical considerations for policymakers, public health officials and researchers when developing, implementing and evaluating opioid-focused AD programs. Additional research is needed to confirm the findings in this dissertation. Replication of these studies in other clinician specialties and in other health systems located in more geographically diverse regions would help to support the burgeoning evidence base for educational outreach programs and their utility in modifying controlled substance prescribing behavior.

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VII. Vita

EDUCATION

- **University of Illinois at Chicago, Graduate College, Chicago, IL**
  Department of Pharmacy Systems, Outcomes & Policy
  PhD Candidate, Pharmacoepidemiology
  08/2016-12/2019
- **University of Illinois at Chicago College of Pharmacy, Chicago, IL**
  Doctor of Pharmacy (PharmD)
  08/2012-05/2016
- **University of Missouri, Columbia, MO**
  Bachelor of Science (BS), Biological Sciences
  09/2008-05/2012

LICENSURE AND CERTIFICATIONS

- Registered IL Pharmacist License No. 051.299446
  03/2018-03/2020

PROFESSIONAL EXPERIENCE

- **Health Economics and Outcomes Research Consultant**
  AbbVie Inc. | *North Chicago, IL*
  05/2019 – Present
  - Supports the Global Hepatitis C Virus (HCV) HEOR team to develop a framework for successful HCV elimination
  - Works cross-functionally with Global Medical Affairs and Marketing teams to develop strategies to critically appraise HCV elimination project proposals from external affiliates
  - Conducts in-depth and comprehensive literature reviews to identify innovative and effective approaches to achieve HCV elimination and communicates the findings to the Global HCV team to inform future efforts
- **UIC – Takeda Health Economics and Outcomes Research Postdoctoral Fellowship**
  University of Illinois College of Pharmacy | *Chicago, IL*
  Takeda Pharmaceuticals, Inc. | *Deerfield, IL*
  07/2016 – 06/2018
  - Leveraged real-world evidence to inform the direction of strategic plans for US Medical Affairs and Payer Marketing teams
  - Supported the execution of HEOR studies (e.g. burden of illness studies, literature reviews, treatment patterns, quality of care, etc.) to demonstrate the value of Takeda products and inform value-based contracting initiatives
  - Delivered presentations of executive summaries on Takeda products to US Medical Affairs and Regulatory Affairs in anticipation of the fluctuating regulatory environment

- Managed and reviewed protocols for HEOR studies conducted internally and externally in a timely manner to ensure protocol accuracy
- Collaborated cross-functionally with US Medical Affairs, Regulatory Affairs, Payer Marketing, and Commercial/Product Development teams to ensure the value of Takeda products were recognized and effectively communicated to external stakeholders

- **Registered Pharmacist**
  Jewel-Osco Pharmacy | *Lombard, IL*
  06/2016 - Present
  - Implements company initiatives to increase profitability
  - Actively participates in and supports clinical services
  - Supervises pharmacy technicians, clerks, and pharmacy interns
  - Upholds operational standards including performance metrics, safety, and compliance
- **Research Consultant**
  eMAX Health | *White Plains, NY*
  10/2016 – 02/2017
  - Developed comprehensive search strategies to identify all relevant literature for a systematic review assessing how “Hypoglycemia leads to Reduced Persistency and Adherence to Insulin in patients with Type 2 Diabetes Mellitus”
  - Provided clinical expertise to inform research team on effective and inclusive search terms and strategies for systematic reviews of metabolic and cardiovascular therapeutic areas
- ***Pharmacy Extern***
  University of Illinois Hospital & Health Sciences System | *Chicago, IL*
  12/2012 – 05/2015
  - Communicated daily with providers and counsel patients relaying pertinent information
  - Collected data from patients and providers used for research purposes
  - Performed monthly audits of medication inventories of all Mile Square Health Center clinics
  - Prepared and updated emergency drug boxes for all Mile Square Health Center clinics
  - Assisted low-income patients with obtaining their medications by enrolling them into the medication assistance program
  - Accurately entered and update patient information on the pharmacy computer system
  - Compounded and reconstituted drug products
  - Continuously updated all drug information resources
- **Pharmacy Technician**
  Kmart Pharmacy | *Homewood, IL*
  05/2012 – 12/2012
  - Processed and filled patient prescriptions
  - Assisted patients when picking up prescriptions
  - Monitored and removed expired drugs from inventory

RESEARCH EXPERIENCE

- **Research Assistant**
  University of Illinois at Chicago, Graduate College | Chicago, IL
  Department of Pharmacy Systems, Outcomes & Policy
  - **Impact of Academic Detailing on Opioid Prescribing Patterns in the Chicagoland Region (PhD Thesis)** 04/2018 – Present
    - The aim of this thesis is to examine the impact of an academic detailing program on opioid prescribing activities among primary care providers in the Chicagoland region.
  - **Impact of Academic Detailing in the Chicagoland Region: A pilot study**
    04/2018 – Present
    - The aim of this project was to assess the feasibility of an educational outreach program among primary care providers on the CDC Guideline for Prescribing Opioids for Chronic Pain through academic detailing visits and then evaluate the impact of academic detailing on primary care providers' opioid prescribing patterns.
    - My role was to train a team of graduate and doctor of pharmacy students on proper academic detailing techniques and to coordinate and manage academic detailing visits with nearly 200 primary care providers dispersed throughout the Chicagoland region.
  - **Associations between Chemo-immunotherapy and Impaired Cognition among Older Patients with Non-Hodgkin Lymphoma**
    01/2017- Present
    - The aim of this research was to gain experience in conducting statistical analyses via epidemiologic computing platforms (e.g. SAS, Stata 14, etc.) using secondary data from SEER-Medicare and manuscript preparation for academic journals.
    - My role included study design development, data analysis and interpretation, and manuscript preparation for the Journal of Geriatric Oncology.
  - **The United States EQ-5D-5L Valuation Study**
    01/2017- 09/2017
    - The aim of this project was to develop an EQ-5D-5L value set for the US general population which may be used to inform reimbursement decisions among payers across the US.
    - My role included coordinating the recruitment of participants, managing the conduct of computer-assisted face-to-face interviews by our research team, and assisting in data analysis.
  - **The FDA Unapproved Drug Initiative**
    07/2016- 07/2017
    - The aim of this project was to measure the impact on prices, expenditures, and quantities sold, for drugs approved under the FDA Unapproved Drug Initiative.

- My role included data management and analysis using the IQVIA National Sales Perspective database to analyze trends in total expenditures, units sold, and price/unit for various drugs.

TEACHING EXPERIENCE

- **Teaching Assistant**
  University of Illinois at Chicago, Graduate College | Chicago, IL
  Department of Pharmacy Systems, Outcomes & Policy
  01/2017–05/2017
  - Facilitated PHAR 354 (Pharmacoeconomics) recitations for 3rd-year Doctor of Pharmacy Students on introductory concepts of pharmacoeconomics

PUBLICATIONS

- Monteiro A, Smart M, **Saffore CD**, Lee TA, Fischer MA, Pickard AS. Development of a Measure Prescriber Satisfaction Academic Detailing. Value in Health. Volume 22, Supplement 2, May 2019.
- Smart M, Monteiro A, **Saffore CD**, Lee TA, Fischer MA, Ruseva A, Pickard AS. Initial Development of an Instrument to Assess the Effectiveness of Academic Detailing Visits. Value in Health. Volume 22, Supplement 2, May 2019.
- Sharma D, Schumock GT, **Saffore CD**, Edwards SA, Walton SM. Estimating the Impact of Food and Drug Administration's Unapproved Drug Initiative on Drug Prices and Sales. Therapeutic Innovation & Regulatory Science. May 2019.
- Sharma D, Schumock GT, **Saffore CD**, Edwards SA, Walton S. Estimating the Impact of the Food and Drug Administration (FDA)'s Unapproved Drug Initiative (UDI) on Drug Prices and Expenditures. Therapeutic Innovation & Regulatory Science. February 22, 2019.
- Guadamuz J, Ozenberger K, Qato D, Ko N, **Saffore CD**, Adimadhyam S, Cha A, Sweiss K, Patel PR, Chiu B, Calip GS. Mediation analyses of socioeconomic factors determining racial differences in the treatment of elderly diffuse large B-cell lymphoma. Medical Care (under review). November 6, 2018.
- **Saffore CD**, Ko N, Holmes H, Patel PR, Sweiss K, Adimadhyam S, Chiu B, Calip GS. Treatment of Older Diffuse Large B-Cell Lymphoma Patients with Mild Cognitive Impairment or Dementia. Journal of Geriatric Oncology. September 5, 2018.
- **Saffore CD**, Guadamuz J, Ozenberger K, Adimadhyam S, Calip GS. Racial Differences in the Prevalence of Cognitive Impairments and Dementia, Utilization of Chemoimmunotherapy and Mortality in Elderly Diffuse Large B-Cell Lymphoma Patients. Value in Health 20(9): A520. October 2017.
- Sharma D, **Saffore CD**, Schumock GT, Walton SM. Measuring The Impact Of The Food And Drug Administration (FDA) Unapproved Drug Initiative (UDI) On Drug Prices And Expenditures. Value in Health 20(9):A655. October 2017.

PRESENTATIONS

- **Saffore CD**, Chiu B, Calip GS. Association between Chemo-Immunotherapy and Development of Mild Cognitive Impairment or Dementia in Older Adults with Non-

Hodgkin Lymphoma. Poster presentation at the ISPOR 24th Annual International Meeting in New Orleans, LA, May 19, 2019.

- **Saffore CD**, Pickard AS, Lee TA. Tailored Approaches to Opioid-related Academic Detailing of Urban and Rural Prescribers. Oral presentation at the 7th Rx Drug Abuse & Heroin Summit in Atlanta, GA, April 24, 2019.
- **Saffore CD**, Ko N, Holmes H, Patel PR, Sweiss K, Adimadhyam S, Chiu B, Calip GS. Treatment of older patients with diffuse large B-cell lymphoma and mild cognitive impairment or dementia. Oral presentation at the 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) in Prague, Czech Republic, August 28, 2018
- **Saffore CD,** Monteiro A, Smart M, Ruseva A, Lee TA, Pickard AS. Development of an Instrument to Assess Academic Detailer's Experience with Academic Detailing Visits. Oral presentation at the 18th Midwest Social and Administrative Pharmacy Conference in Madison, WI, August 16, 2018.
- **Saffore CD**, Guadamuz J, Ozenberger K, Adimadhyam S, Calip GS. Racial Differences in the Prevalence of Cognitive Impairments and Dementia, Utilization of Chemo-immunotherapy and Mortality in Elderly Diffuse Large B-Cell Lymphoma Patients. Poster presentation at the ISPOR 20th Annual European Congress in Glasgow, Scotland, November 6, 2017.
- **Saffore CD**, Bellfi L, Edwards SA, Walton S, Schumock GT. Impact of the FDA's Unapproved Drug Initiative on Expenditures for Oral Colchicine in the United States. Poster presentation at the ISPOR 22nd Annual International Meeting in Boston, MA, May 22, 2017.

AWARDS & HONORS

- **University of Illinois at Chicago College of Pharmacy**
  - Rho Chi – AFPE Clinical Research Scholarship, 2017
  - Rho Chi – AFPE First Year Graduate Fellowship, 2016
  - Dr. Martin Luther King Jr. Scholarship, 2016
  - W.E van Doren Scholarship, 2016
  - TEVA Pharmaceutical USA Outstanding Student Award, 2016
  - Chancellor's Student Service and Leadership Award, 2015
  - Eden Life Scholarship, 2015
  - Dean's List, 2012-2016
- **University of Missouri**
  - Diversity Award Scholarship, 2008-2012
  - MU Grant, 2008-2009

PROFESSIONAL AFFILIATIONS

- International Society for Pharmacoeconomics and Outcomes Research, 2016-Present
- International Society for Pharmacoepidemiology, 2016-Present
- *Rho Chi* Honors Fraternity, 2014-Present
- International Society of Pharmaceutical Engineers, 2014-2015

- *Phi Delta Chi* Pharmaceutical Fraternity, 2012-2016

REFERENCES

- Available upon request