FACTORS INFLUENCING CLINICIAN DECISION MAKING REGARDING OPIOID PRESCRIBING AND PAIN MANAGEMENT

by

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ABSTRACT

MEGHAN KUSPER WALLY. Factors Influencing Clinician Decision Making Regarding Opioid Prescribing and Pain Management.
(Under the direction of DR. MICHAEL E. THOMPSON)

Opioid overdose deaths have increased substantially over the past fifteen years. However, the position and beliefs of the medical community regarding opioids over time has not been described. Despite the proliferation of guidelines, interventions, and policies aimed at the medical community, the extent to which these actions have impacted clinical decision making and prescribing behavior has not been rigorously studied, accounting for simultaneous interventions and the nested structure of healthcare delivery systems. To address this gap, I characterized the experience of the medical community and measured the multi-level factors influencing opioid prescribing within the context of legislation and clinical decision support interventions. A content analysis of letters to the editor in the *Journal of the American Medical Association* between 2008 and 2018 demonstrated physicians overall valued balance between pain management and adverse effects of opioid prescribing. Physicians took ownership of their role in the epidemic, but called upon the government and community to help take action to address the issue. I found environmental context and resources to be a relevant theme. These findings framed and grounded my subsequent quantitative analyses. Among patients with an acute musculoskeletal injury in a large healthcare system (n=12,918), I found there was a 17.7% increase in prescriptions written for 7 days or less after the STOP Act was implemented ($p<0.001$), even after adjusting for the existing trend with an interrupted time series design. After implementation of the STOP Act, opioids were prescribed for less than 7 days in 77.1% of encounters, with 30% of variation accounted for by physician and another 9% by facility. I also

assessed the impact of a clinical decision support on safe opioid prescribing, operationalized as a composite score of several behaviors in response to the intervention (e.g., prescribing naloxone, initiating a pain agreement). This intervention had a statistically significant but small impact on the percent of patients with chronic musculoskeletal conditions (n=1,290,746) receiving an opioid, with the percent being 1.6% lower than before the intervention. There was not a change in the average dose of opioid prescriptions associated with the intervention. Overall, the median safe opioid prescribing score in the post-intervention period was 77.1%, with 24% of the variation accounted for by practice site. Collectively, this research and resulting manuscripts present a sophisticated and nuanced understanding of the multi-level factors which influence guideline-concordant opioid prescribing. These data can be used to design and tailor additional interventions for populations where adherence to guidelines is low. The findings also demonstrate the necessity for more advanced modeling to account for the nested organization of healthcare delivery and team-based nature of clinical care, as well as rigorous research to explore the effect of interventions across sectors happening simultaneously to efficiently guide decision making and policy.

DEDICATION

This dissertation is dedicated to my husband, James. You have been my strongest supporter throughout more than seven years of higher education while reminding me to take time for myself, family, and friends. I also dedicate this dissertation to my daughter, Melissa. You have been my inspiration to persevere and have given me a reason to smile every day. I look forward to watching you pursue your own dreams.

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LIST OF ABBREVIATIONS

AAOS	American Academy of Orthopaedic Surgeons
ACCME	Accreditation Council for Continuing Medical Education
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CDC	Centers for Disease Control and Prevention
CPG	Clinical Practice Guidelines
DEA	Drug Enforcement Agency
EBM	Evidence-Based Medicine
ED	Emergency Department
EMR	Electronic Medical Record
FDA	Food and Drug Administration
ICD	International Classification of Disease
JAMA	*Journal of the American Medical Association*
MME	Morphine Milligram Equivalents
MSK	Musculoskeletal
PDMP	Prescription Drug Monitoring Program
PRIMUM	Prescription Reporting with Immediate Medication Utilization Mapping
STOP	Strengthen Opioid Misuse Prevention
TDF	Theoretical Domains Framework

CHAPTER 1: INTRODUCTION

Opioid Prescribing

Mortality from drug overdoses in the United States has tripled in the past fifteen years, with over 180,000 people dying from prescription drug overdoses each year.[1,2] This epidemic has had a tremendous impact on the country, with opioid-related deaths contributing to a dramatic decline of 0.21 years in average life expectancy among Americans from 2014 to 2015.[3] Opioid overdose deaths and opioid prescribing rates are correlated. As the medical community prioritized and focused on treating patient pain, opioid prescriptions increased considerably from 2006 until 2012,[4] while reported pain did not decrease.[5]

Clinical Decision Making and Clinical Practice Guidelines

Clinical decision-making is a complex process which involves synthesizing biomedical knowledge, weighing probabilities, balancing risk and benefit, and drawing upon intuition and personal experience.[6] To guide clinical decision-making, the federal government has invested significantly in comparative effectiveness research.[7] Clinical practice guidelines (CPGs) are recommendations intended to guide clinicians and patient decisions in specific clinical circumstances, based upon a systematic review of scientific evidence."[8] CPGs often rely on comparative effectiveness research and other scientific evidence, and therefore, should lead to change in clinical practice to favor the more efficacious, beneficial, or cost-effective treatment. While the recommendations included in CPGs should ease the clinical decision-making process, the literature supports the concept of a "research-practice gap", indicating that clinicians do not consistently make treatment decisions based upon current evidence or CPGs.[9] In fact, U.S. adults receive less than 55% of recommended care.[10] Individual clinician decision-making is proposed as a reason for the lack of uptake of CPGs;[11] therefore, the overwhelming majority of

interventions thus far to increase adherence to CPGs has focused on changing individual clinician behavior.[12] These interventions include clinical decision support, continuing education, and audits or dashboards. Some clinical decision support interventions have demonstrated efficacy,[13-20] while others have null mixed results.[21-25] Continuing education has a strong evidence base in general,[26] and the existing literature does demonstrate an impact on opioid prescribing outcomes, especially when combined with decision support or legislation.[27,28] Audit and feedback techniques as well as dashboards have also been successful at influencing opioid prescribing outcomes through peer comparison.[13,18,19,29,30]

The Centers for Disease Control and Prevention (CDC) released a CPG in 2016 for opioid prescribing for chronic pain.[31] The guideline provides information regarding: "determining when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use".[31] One study did find a significant decrease in high dosage prescriptions, overlapping opioid and benzodiazepine prescriptions, and overall opioid prescribing rate upon release of the guideline across the United States.[32] Guideline concordant opioid prescribing also improved in the emergency department setting of an academic medical center following the release of the guideline.[33] Still, less than 70% of physicians at an academic medical center were aware of these guidelines in 2018.[34]

In addition to CPGs, federal and state governments have used policy to address the crisis.[35] Federal agencies who have enacted policies to regulate opioids include the Food and Drug Administration (FDA), the Drug Enforcement Agency (DEA), and the Department of Justice. These agencies have made progress to address pill mills and implement prescription drug monitoring programs (PDMPs). The FDA has added warnings on drug labels and played a role in

approving new medications. At the local level, states have required physician education, mandated review of PDMPs, and created standing orders for naloxone to allow access without a prescription. Currently, states are in the process of litigation against pharmaceutical companies for their role in the epidemic.

Theoretical Framework

While clinical information contributes to clinical decision-making, numerous nonclinical factors also influence decision-making. In general, nonclinical factors may include patient characteristics, clinician characteristics, and systematic factors.[6,36-38] Hajjaj et al. described patient characteristics, such as demographics and socioeconomic status, current quality of life, and expectations and preferences, as influencing clinical decisions.[6] Physician characteristics, including interaction with the professional community, personality type, demographics, and relationships with consulting physicians, also influence decisions.[6,37]

Literature assessing physician knowledge of appropriate opioid prescribing, opioid clinical practice guidelines, and/or opioid regulations is sparse. Less than half of orthopaedic residency programs require education on opioids and up to 90% of residents do not receive formal training;[39,40] however, simple educational programs have been found effective at improving opioid prescribing practices.[30,41,42] Qualitative research has also highlighted the lack of formal education and lack of awareness of the long-term consequences of opioids among orthopaedic surgeons.[43]

In comparison to individual clinician knowledge, environmental context and resources highlights external factors which can influence physician behavior. Some factors include the type of practice, physician organization, geographical location, resources of the practice or community, management policies, treatment cost, reimbursement, interactions with

pharmaceutical companies, the market environment, and public policy.[6,37] Reschovsky et al. described the potential tension between acting in the patient's best interest and the conscious or unconscious influence of organizational structure and policies on their treatment decisions.[37] For example, high patient volume and short visits may force the clinician to rely on oversimplified heuristics.[37] Market forces have the potential to alter decision-making if physicians are pressured to make decisions which retain patients and maintain high patient satisfaction.[37] Current knowledge of nonclinical influences on pain management or opioid prescribing is limited and almost entirely focused on patient characteristics and behaviors, clinician characteristics, or patient-provider communication.[44-47] However, a qualitative study of emergency physicians found that practice environment was one of the top three factors influencing their opioid prescribing decisions.[48]

Because clinical decision-making is a complex process influenced by a myriad of factors, a conceptual or theoretical framework is useful when studying physician behavior in response to clinical practice guidelines. However, of published studies describing CPG implementation or evaluation, less than half are based on theory.[49] The most commonly applied theories are the Theory of Planned Behavior (38%) and the Theoretical Domains Framework (24%).[49]

The Theoretical Domains Framework (TDF) was developed by Michie et al. to outline important theoretical constructs for studying the implementation of CPGs and developing effective implementation strategies for clinical practice change.[50] Drawing from motivational, action, and organizational theories, Michie et al. identified relevant theories and constructs and simplified them into theoretical domains.[50] After rigorous content validation and revision, these domains include: "1) knowledge; 2) skills; 3) social/professional role and identity; 4) beliefs about capabilities; 5) optimism; 6) beliefs about consequences; 7) reinforcement; 8) intentions;

9) goals; 10) memory, attention and decision processes; 11) environmental context and resources; 12) social influences; 13) emotion; and 14) behavioral regulation".[51] Each of these domains has multiple component constructs which can influence clinical decision making. For example, beliefs about capabilities includes constructs such as self-efficacy, self-esteem, perceived competence, empowerment, and control. In the context of opioid prescribing, lack of confidence in alternative pain management strategies is an example of a belief about capability. The social influences domain includes constructs such as social support, group conformity, social pressure, social comparison, and organizational commitment. A resident physician may feel follow the same treatment plan as a trusted senior mentor, for example. The TDF was designed to be very practical; therefore, it is most useful to apply the framework to a specific clinical topic, such as the CDC CPG.

Significance

The culture of medicine has largely shifted from clinical intuition and experience toward evidence-based medicine (EBM) and CPGs.[6] However, the uptake of EBM and CPGs is not widespread.[8,9] Without studying the factors influencing clinical decision making regarding clinical practice guidelines, CPGs and comparative effectiveness research are limited in their ability to effect change. Initiatives to change physician behavior are not typically theory-driven, and there is a lack of a theoretical knowledge base for understanding physician behavior altogether.[52,53]

Clinical practice is a team-based effort which occurs within a larger organizational setting. Advanced care practitioners and nurses support physicians in their practice and often carry out the treatment recommended by the physician. In addition, many medical conditions require multidisciplinary coordination between general practitioners and specialists. Finally,

most clinicians work within large, complex healthcare systems which have their own organizational culture, policies, and procedures which can impact clinical decisions. Ignoring the context in which physician clinical decision-making occurs limits the applicability of findings.

The pace of research has increased in the past few decades, making it very difficult for clinicians to learn and apply new findings and evidence.[54] Therefore, CPGs are critical tools for clinicians to make sense of the abundance of literature and change their practice accordingly. However, CPGs are often not implemented,[8,9] despite the prevalence of interventions targeting individual clinicians.

By understanding the factors influencing clinical decisions, it is more likely that we can successfully improve adherence to and use of CPGs and bridge the gap between research and practice. Without such scientific inquiry, CPGs and comparative effectiveness research are limited in their ability to effect clinician behavior change and improve healthcare delivery. This study is significant because it illuminates factors both within and beyond the individual clinician that impact CPG adherence, informing modification of clinicians, teams, systems, and structures to promote guideline-concordant care, ultimately improving patient outcomes.

In summary, the extent to which guidelines and policies have influenced clinical decision making regarding opioid prescribing remains largely unknown. The impact of a clinical decision support intervention to operationalize and implement these guidelines on an organizational scale has not been described or evaluated. Within the context of clinical decision support and legislation, thoroughly understanding the multi-level factors influencing prescribing decisions rather than focusing solely on individual clinicians is necessary. Finally, thorough theoretical knowledge for understanding physician behavior in this context is lacking.

Researcher Statement

I am a researcher trained in public health who studies healthcare delivery and patient outcomes. My primary interest is in understanding the clinical decision-making process in the context of the patient-provider relationship and the larger organizational structure and culture of healthcare systems. A significant focus of my research so far has been clinical decision support for clinicians and guideline implementation surrounding opioid prescribing. I have prior working experience as a nurse assistant and am currently employed by a healthcare system in orthopaedic surgery. Because I work in the healthcare setting, I have an emic perspective regarding the research question.[55] Finally, I approach research with the goal to produce practical knowledge which can be used to change and improve healthcare. Therefore, I aim to identify barriers and facilitators of implementation of CPGs, which influenced my choice of theoretical framework and methodology.

Dissertation Research

The proposed research addresses gaps in knowledge regarding the physician experience of the opioid epidemic and associated legislation, regulations, and interventions. It also provides a sophisticated understanding of the multi-level factors which influence opioid prescribing in accordance with CPGs in the context of legislation and clinical decision support interventions.

I conducted a mixed-methods study to gain a rich understanding of factors influencing clinical decision making regarding opioid prescribing. The first study, entitled “Physician Experience of The Opioid Crisis: A Content Analysis of Letters to the Editor”, was a qualitative content analysis of letters to the editor in academic medical journals on opioid prescribing. It addressed the following research questions, 1) “Which positions regarding the opioid epidemic are prevalent among the medical community”?; 2) “To what extent is there a professional consensus on these positions?”; and 3) “How has professional discourse changed over time?” I

analyzed letters to the editor from a prominent academic medical journal over the past ten years related to opioids. I used provisional codes based on the Theoretical Domains Framework as well as themes which emerged during data analysis. I selected *Social Science & Medicine* as the target journal for this manuscript. This journal aims to publish social science research that is relevant to healthcare, clinical practice, and health policy. The journal also published a similar content analysis of Letters to the Editor regarding Medicaid expansion. A summary of requirements for each of my selected target journals is included in Table 1A.

TABLE 1A. MANUSCRIPT REQUIREMENTS FOR SELECTED TARGET JOURNALS

	Social Science & Medicine	*Journal of Orthopaedic Trauma*	*The Journal of Bone and Joint Surgery*
Word Count	9000 including abstract, tables, figures, and references	3000 excluding abstract and references	3000 including abstract, excluding references and figure legends
Abstract Word Count	300	250	325
Abstract Headings	Not specified	Objectives, Design, Setting, Patients/Participants, Intervention, Main Outcome Measurements, Results, Conclusions, Level of Evidence	Background, Methods, Results, Conclusions, Level of Evidence
Manuscript Text Sections	Introduction, Materials and Methods, Results, Conclusions	Introduction, Materials and Methods, Results, Discussion	Introduction, Materials and Methods, Source of Funding, Results, Discussion
Number of Tables and Figures	Not specified	Not specified	Not specified
Reference Style	No specified style required at submission stage. Use of DOI is highly encouraged.	American Medical Association, 10th edition Numbered consecutively in order they appear in text For more than 3 authors, name first three, then use et al.	PubMed/Index Medicus format
Other	Must provide 3 potential reviewers		$250 submission fee Limit of 6 authors

The remaining two studies utilized an existing dataset of opioid prescriptions at a large healthcare system and the data associated with the launch of a prospective clinical decision support intervention.

The second study, entitled "Opioid Prescribing for Acute and Post-Surgical Musculoskeletal Pain: The Effect of the Strengthen Opioid Misuse Prevention (STOP) Act", addressed the research questions: 1) "Was implementation of the STOP Act associated with an increase in the percent of prescriptions written for 7 days or less among patients with acute or post-surgical musculoskeletal conditions?", and 2) "Which patient, prescriber, and facility characteristics are associated with adherence with STOP Act legislation?". I conducted an interrupted time series analysis to answer the first research question. To address the second research question, I applied a hierarchical logistic regression model to predict the odds of prescriptions of 7 days or less. This manuscript focuses on musculoskeletal clinicians treating acute injuries, so I selected the *Journal of Orthopaedic Trauma* as the target journal. This journal focuses on hard and soft tissue trauma and musculoskeletal injuries, and the target audience is musculoskeletal clinicians and healthcare administrators.

The third study, entitled "Opioid Prescribing for Chronic Musculoskeletal Conditions: Trends over Time and Implementation of Safe Opioid Prescribing Practices", addressed the following research questions: 1) "Was implementation of a clinical decision support intervention associated with a decrease in the percent of chronic musculoskeletal pain patients receiving opioid prescriptions and/or average dose?" and 2) "Which prescriber and facility characteristics are associated with adherence with implementation of safe opioid prescribing practices"? I conducted an interrupted time series analysis to answer the first research question. To address the second research question, I applied a hierarchical linear regression model to predict safe opioid

prescribing as measured by a composite score of five behaviors included in the CDC CPG. This manuscript focuses on clinicians treating common chronic musculoskeletal conditions, so I selected the *Journal of Bone & Joint Surgery* as the target journal. This journal's mission is to improve musculoskeletal health by providing information for clinicians, researchers, and orthopaedic care teams. It is a commonly read journal for orthopaedic surgeons of all subspecialties.

The results of this research can be integrated to inform future interventions to address opioid safety. The qualitative results can inform the development of policies and programs which are most likely to be successful at effecting guideline-concordant opioid prescribing. The results will determine the impact of local legislation and illuminate multilevel factors that impact adherence to opioid prescribing legislation. This information can inform interventions for clinicians, teams, systems, and/or structures to promote adherence and optimize the impact of legislation. This research determined the impact of a clinical decision support intervention and identify factors that impact safe opioid prescribing behaviors. These results can be used to modify and iteratively improve the existing intervention as well as inform dissemination efforts to other healthcare systems.

CHAPTER 2: PHYSICIAN EXPERIENCE OF THE OPIOID CRISIS: A CONTENT ANALYSIS OF LETTERS TO THE EDITOR

Introduction

Drug overdose deaths are a significant cause of death in the United States, with over 70,000 deaths in 2019.[1] An opioid was involved in over two-thirds of these deaths.[2] However, in recent years, most opioid-related deaths have resulted from illicit and synthetic opioids rather than prescription opioids. Furthermore, there was a 2.0% decrease in opioid overdose deaths in the US from 2017 to 2018 and a 13.5% decrease in prescription opioid deaths specifically.[2] However, overdose death rates including synthetic opioids increased by 10% and account for almost three-fourths of opioid deaths.[1,3] Despite encouraging trends, provisional data from 2020 indicate a historic 30% increase in drug overdose deaths, with over 93,000 people dying.[4]

Multiple efforts have been employed to address this crisis. For example, changes have been made to law enforcement, drug policies, educational programs, and harm reduction and substance use treatment programming. Many efforts have also focused on prescribing practices of physicians. Some of these include the development of prescription drug monitoring programs, legislation regarding the dose or duration of prescriptions allowed, clinical practice guidelines, and even criminal charges against doctors accused of inappropriate prescribing.[5-7] The concurrent decrease in prescription opioid deaths and increase in illicit opioid deaths suggests that interventions targeting the healthcare community and prescribers have been successful.[2] However, there is a paucity of evidence about the physician experience of this epidemic over time.

Developing policies and programs which are most likely to be successful for effecting and maintaining guideline-concordant and evidence-based opioid prescribing requires knowledge

about the physician experience of this epidemic. For example, addressing prescriber concerns and respecting their professional role and expertise is a critical step in effective program or policy development. As an exploratory first step, I conducted a qualitative analysis of letters published in the *Journal of the American Medical Association (JAMA).* The purpose of this study was to describe the public discourse around opioids among the medical community during the peak of the opioid epidemic. I also explored which theoretical domains might be relevant to opioid prescribing. My research questions were: 1) "Which positions regarding the opioid epidemic are prevalent among the medical community?"; 2) "To what extent is there a professional consensus on these positions?"; and 3) "How has professional discourse changed over time?"

Conceptual Framework

The Theoretical Domains Framework (TDF) is based on a large body of literature on behavior change in social and behavioral sciences[8-12] and includes 14 domains. I chose this guiding framework because opioid prescribing should be evidence-based, clinical practice guidelines for opioid prescribing exist, and the opioid epidemic has led to a proliferation of rules and regulations on physicians to effect clinical practice change.

Several studies specifically used the TDF to identify factors influencing prescribing behaviors among surgical oncologists using physician interviews. They found five TDF domains to be particularly relevant to opioid prescribing: environmental context and resources, social influences, beliefs about consequences, social/professional role and identity, and goals.[13] Another study found knowledge, environmental context and resources, and professional role/identity to be most applicable regarding the management of postoperative pain among surgeons and primary care physicians.[14] Unrelated to the TDF, a recent qualitative evidence synthesis of studies exploring healthcare professionals' experience of treating adults with chronic

non-cancer pain (n=17) and identified six overarching themes, including ‘Should I, shouldn’t I?’, ‘Pain is Pain’, ‘Walking a Fine Line’, ‘Social guardianship’, ‘Moral boundary work’, and ‘Regulations and Guidelines’. Overall, their conceptual model illustrates a balance between the decision to prescribe (‘Pain is Pain’) and not to prescribe (‘Social Guardianship’), with the other factors tipping the scale in one direction or the other.[15]

While previous qualitative research has assessed the beliefs, attitudes, and experience of individual physicians in relation to opioids[15,16], no studies have assessed the professional discourse through a review of letters published in prestigious medical journals. However, content analysis of letters to the editor has been used to assess physicians’ and the lay public’s opinions regarding Medicaid expansion as well as academic discourse surrounding research on firearms.[17,18] Assessing the public discourse among physicians can supplement existing research on individual clinician experiences by providing an understanding of the larger context of the medical community as a whole, including relevant theoretical domains.

Methods

As the purpose of this study was exploratory, a qualitative design was a useful and appropriate approach to learn about the public discourse around opioids among the medical community during the peak of the opioid epidemic. To explore the research questions, I conducted a systematic search for letters to the editor published in *JAMA.* I chose this journal because it has a large readership across medical specialties, is associated with a medical professional society that sets norms and protocols, and is among the top tier of medical journals by impact factor.[19] I conducted content analysis of these letters to the editor to describe the prevalent positions on the opioid epidemic, the degree of professional consensus, and whether discourse changed over time. These letters are important because they have the ability to shape

opinion in the larger medical field. This methodology allows for an analysis of trends over time as the climate around this topic has changed over the past decade. Finally, letters to the editor published in academic journals have been reviewed by editorial boards, indicating these opinions are at least important enough or widespread enough to be printed.

Data Collection

I used the following search term in PubMed to identify the letters: (((opioid) AND "jama"[Journal])) AND letter [Publication Type]. I limited the letters to 10 years (2008-2018), which represented the peak of the opioid crisis in the United States (n=146). I eliminated articles which did not discuss issues of addiction, opioid misuse, dependence, or persistent use. I also eliminated articles which were scientific critiques in response to published research articles. First, I screened abstracts to determine eligibility. After screening abstracts, I excluded 54 articles. Then, I reviewed the full text of the remaining 92 articles. Ultimately, I included 39 letters (10 original letters and 29 responses).

Data Analysis

I coded each letter to the editor by hand. I used the process of abduction[20] by incorporating both theory-informed a priori codes as well as themes which emerged from the data. First cycle coding included provisional, a priori codes[21] for each domain of the Theoretical Domains Framework (e.g., beliefs about capabilities, environmental context and resources). The Theoretical Domains Framework was developed by Michie et al. to outline important theoretical constructs for studying the implementation of evidence-based medical practice and developing strategies for effective implementation of clinical practice change.[12] However, the only domain that was frequently present (in more than 3 letters) was environmental context and resources. Therefore, this paper focuses on the codes identified through first cycle open coding.

I also used a combination of in vivo and open coding techniques.[21] These codes emerged from the data during the coding process. I performed sequential data analysis[21], in which my analysis plan emerged and evolved as I coded the data, revised my codebook, and recoded the data (See Appendix 2A for final codebook). Finally, I maintained a record of all raw data, memos, codebook versions, study procedures, and a reflexive journal to facilitate an inquiry audit and optimal rigor.[22] Thorough documentation of the research process and the data which led to my findings builds dependability and confirmability.[22]

During the first round of coding[23], three overall positions emerged across the letters: 1) authors advocating for limiting the use of opioids, given the consequences of addiction and overdose ("opioid averse"); 2) authors warning that a drastic change in opioid prescribing may result in insufficient treatment for and stigma toward chronic pain patients ("opioid defense"); and 3) authors cautioning that a "balanced" approach between these two extremes is needed ("balanced"). However, some letters presented facts without any text supporting one of the viewpoints above. These letters were coded as "neutral". I used these codes to categorize the position of each letter and response according to these categories. Each letter was coded as only one of these four categories. For example, a letter categorized as "opioid averse" may also have included language regarding "balance".

In addition, during first cycle coding, I found consistent themes of blame and responsibility throughout all the letters. I defined blame as "text which explains how an entity or event contributed to the opioid epidemic", and was framed as past events, while responsibility was defined as "text which calls for a certain group to take action to address the opioid epidemic." In a subsequent round of coding, I further categorized "blame" and "responsibility" to describe the groups who were being blamed or called upon for action: physicians/clinicians,

regulatory agencies, the pharmaceutical industry, government, the healthcare sector, community, and graduate medical education. I coded these themes line by line; each letter could have multiple themes. For analysis, I condensed each theme to indicate whether that letter included that theme or not. For example, if a letter included the "blame-physicians/clinicians" theme four times or if it only included that theme once, I counted it as "yes". Similarly, a letter could include multiple themes (e.g., blame-physicians/clinicians, responsibility-physicians/clinicians, and blame-regulatory agencies). A colleague (TS) reviewed all of the letters. We discussed the coding framework and found that the themes identified in the codebook (Appendix 2A) adequately captured the professional understanding of and response to critical issues related to prescribing opioids. Categorizing a given letter as falling into either the opioid adverse, defense, or balanced category was straightforward. Determining specific targets for blame and responsibility was also straightforward.

To assess patterns in the positions as well as the themes of blame and responsibility, I also included structural coding[24] with objective information about each letter, including the year of publication, the length of the letter, and the training of the author (e.g.., MD, PhD, MPH). If authors had multiple degrees or medical specialties, I included them in multiple categories. I employed internet searches to obtain additional information about the authors, including the institution where they practice, their geographic location (state), and their medical specialty. These data facilitated the comparison of responses across and between groups. Inclusion of the date of publication allowed me to answer the third research question regarding change over time. When coding the responses to the original letter, I categorized the tone and purpose of the response (i.e., agree, disagree) to enable analysis of the second research question regarding consensus.

Results

I identified ten letters, each with at least one response. I also included letters written in response to the CDC Guidelines, even though the original paper was not included because it was not a letter.[25-63] Thus, I included 11 "units". Appendix 2B depicts a profile matrix with information about each letter and its associated responses.[24] Table 2A summarizes the characteristics of the letters and authors. While most of the original letters included multiple authors, half of the responses only included one author. The majority of letters included at least one physician, but all of the original letters included a physician. Among all letters, internal medicine and emergency medicine were the most prevalent medical specialties. The original authors uniquely represented addiction medicine and rheumatology, while the responses uniquely represented anesthesiology, family medicine, physiatry, pain, and oncology. Half of the original letters were authors from government agencies, while the majority of responses were from hospitals/healthcare systems and medical schools or other universities. Most authors were from the Northeastern United States, but there was more diversity among the responses.

Research Question 1

I also used a profile matrix to depict the author characteristics along with their position on opioid prescribing (Table 2B).[24] Overall, 7 (18%) of letters were "opioid averse"; 13 (33%) were "balanced"; 1 (3%) was "opioid defense", and many (46%) were neutral. The "opioid averse" letters were often original letters, while the "balanced" letters were often the responses to the original authors. The sole "opioid defense" letter was a response written by one author. The only letters that did not include a physician were the neutral ones. The letters written by pain or oncology specialists were never "opioid averse". The patterns by specialty were fairly similar between "opioid averse" and "balanced". Most of the "opioid averse" authors were affiliated

with a university, while the "balanced" authors represented a more diverse group. No pattern by region emerged across the positions.

TABLE 2A. PROFILE MATRIX OF LETTERS, BY LETTER TYPE

	Original Letters Only N=10	Responses Only, Excluding Responses by Original Authors N=18	All Letters, Excluding Responses by Original Authors N=28
	N (%)	N (%)	N (%)
Number of Authors			
1	1 (10.0%)	9 (50.0%)	10 (35.7%)
2	5 (50.0%)	6 (33.3%)	11 (39.3%)
≥3	4 (40.0%)	3 (16.7%)	7 (25.0%)
At least one author with MD/DO	10 (100.0%)	15 (83.3%)	25 (89.3%)
Medical Specialty*			
Emergency Medicine	3 (30.0%)	5 (27.8%)	8 (28.6%)
Psychiatry	2 (20.0%)	2 (11.1%)	4 (14.3%)
Internal Medicine	6 (60.0%)	3 (16.7%)	9 (32.1%)
Pediatrics	2 (20.0%)	4 (22.2%)	6 (21.4%)
Anesthesiology	0 (0.0%)	2 (11.1%)	2 (7.1%)
Addiction Medicine	2 (20.0%)	0 (0.0%)	2 (7.1%)
Family Medicine	0 (0.0%)	1 (5.6%)	1 (3.6%)
Physiatry	0 (0.0%)	1 (5.6%)	1 (3.6%)
Pain	0 (0.0%)	3 (16.7%)	3 (10.7%)
Oncology	0 (0.0%)	1 (5.6%)	1 (3.6%)
Rheumatology	1 (10.0%)	0 (0.0%)	1 (3.6%)
Institution Type**			
Government Agency	5 (50.0%)	1 (5.6%)	6 (21.4%)
Medical School	2 (20.0%)	4 (22.2%)	6 (21.4%)
Hospital	1 (10.0%)	6 (33.3%)	7 (25.0%)
Accrediting Agency	1 (10.0%)	1 (5.6%)	2 (7.1%)
University	1 (10.0%)	5 (27.8%)	6 (21.4%)
Pharmaceutical Company	0 (0.0%)	1 (5.6%)	1 (3.6%)
Region			
Midwest	1 (10.0%)	3 (16.7%)	4 (14.3%)
Northeast	7 (70.0%)	8 (44.4%)	15 (53.6%)
Southeast	1 (10.0%)	0 (0.0%)	1 (3.6%)
Southwest	0 (0.0%)	1 (5.6%)	1 (3.6%)
West	0 (0.0%)	1 (5.6%)	1 (3.6%)
Mix	1 (10.0%)	4 (22.2%)	5 (17.9%)
Canada	0 (0.0%)	1 (5.6%)	1 (3.6%)

*These percentages do not add up to 100% because some letters did not include physicians, and some letters included multiple physicians.

**One affiliation was selected for each letter. If authors were from multiple institutions, the first in this list was assigned.

TABLE 2B. PROFILE MATRIX OF LETTERS, BY POSITION

	Opioid Averse N=7	Balanced N=13	Opioid Defense N=1	Neutral N=18
	N (%)	N (%)	N (%)	
Letter Type				
Original	4 (57.1%)	4 (30.8%)	0 (0.0%)	2 (11.1%)
Response	2 (28.6%)	3 (23.1%)	1 (100.0%)	12 (66.7%)
Response by Original Author	1 (14.3%)	6 (46.2%)	0 (0.0%)	4 (22.2%)
Number of Authors				
1	1 (14.3%)	3 (23.1%)	1 (100.0%)	6 (33.3%)
2	4 (57.1%)	6 (46.2%)	0 (0.0%)	6 (33.3%)
≥3	2 (28.6%)	4 (30.8%)	0 (0.0%)	6 (33.3%)
At least one author with MD/DO	7 (100.0%)	13 (100.0%)	1 (100.0%)	15 (83.3%)
Medical Specialty*				
Emergency Medicine	2 (28.6%)	4 (30.8%)	0 (0.0%)	5 (27.8%)
Psychiatry	2 (28.6%)	2 (15.4%)	0 (0.0%)	2 (11.1%)
Internal Medicine	5 (71.4%)	4 (30.8%)	0 (0.0%)	7 (38.9%)
Pediatrics	1 (14.3%)	1 (7.7%)	0 (0.0%)	6 (33.3%)
Anesthesiology	1 (14.3%)	1 (7.7%)	0 (0.0%)	0 (0.0%)
Addiction Medicine	2 (28.6%)	1 (7.7%)	0 (0.0%)	1 (5.6%)
Family Medicine	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Physiatry	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Pain	0 (0.0%)	1 (7.7%)	1 (100.0%)	1 (5.6%)
Oncology	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
Rheumatology	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (5.6%)
Institution Type**				
Government Agency	2 (28.6%)	4 (30.8%)	0 (0.0%)	6 (33.3%)
Medical School	1 (14.3%)	2 (15.4%)	0 (0.0%)	5 (27.8%)
Hospital	1 (14.3%)	4 (30.8%)	1 (100.0%)	2 (11.1%)
Accrediting Agency	0 (0.0%)	2 (15.4%)	0 (0.0%)	1 (5.6%)
University	3 (42.9%)	1 (7.7%)	0 (0.0%)	3 (16.7%)
Pharmaceutical Company	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Region				
Midwest	0 (0.0%)	2 (15.4%)	0 (0.0%)	3 (16.7%)
Northeast	5 (71.4%)	7 (53.8%)	1 (100.0%)	7 (38.9%)
Southeast	1 (14.3%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
Southwest	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
West	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)
Mix	1 (14.3%)	1 (7.7%)	0 (0.0%)	4 (22.2%)
Canada	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)

*Percentages do not equal 100% because some letters did not include physicians, and some letters included multiple physicians.

**One affiliation was selected for each letter. If authors were from multiple institutions, the first in this list was assigned.

Figure 2A depicts the attribution of blame and responsibility across the original letters. Overall, the authors placed the most blame upon physicians for overprescribing. Almost half of letters also attributed blame to regulatory agencies, most notably, the Joint Commission. To illustrate the confluence of these issues, Volkow (Letter 4, Appendix 2B) said:

> …it is also likely that part of this increased abuse is due to much greater access to and availability of opioid analgesics. This is likely to reflect more aggressive management of noncancer pain, facilitated in part by the "regulatory" mandate from the Joint Commission to screen and manage pain, but also by the lingering concerns regarding the safety of nonopioid analgesics…[36]

Dowell (Letter 1, Appendix 2B) similarly said:

> The increase in prescribing occurred in the context of a greater emphasis on treating pain following the efforts by the American Pain Society, the Veterans Health Administration, the Joint Commission and others to increase recognition and management of pain, as well as advocacy by pain societies urging physicians to use opioid more readily for patients with chronic noncancer pain.[25]

While the authors did take on responsibility as physicians in 60% of the letters, they also commonly urged the government and community to take action. Authors occasionally called for physicians to change prescribing patterns, but also highlighted the role of physicians in advocacy and reducing stigma. Olsen (Letter 11, Appendix 2B) argued, "Health care practitioners can counter stigma by adopting accurate, nonjudgmental language to describe this disorder, those it affects, and its therapy with medications."[61] The authors supported government action in the areas of increasing regulation on prescribing, implementing prescription drug monitoring programs, funding research, expanding access to treatment, and collaborating with law

enforcement to address the illicit drug supply. At the community level, authors advocated for harm reduction programs, advocacy for access to treatment, and improved awareness of and responsibility for safe opioid use, storage, overdose prevention, and disposal. A summary matrix with more detailed information for each theme is provided in Appendix 2C.

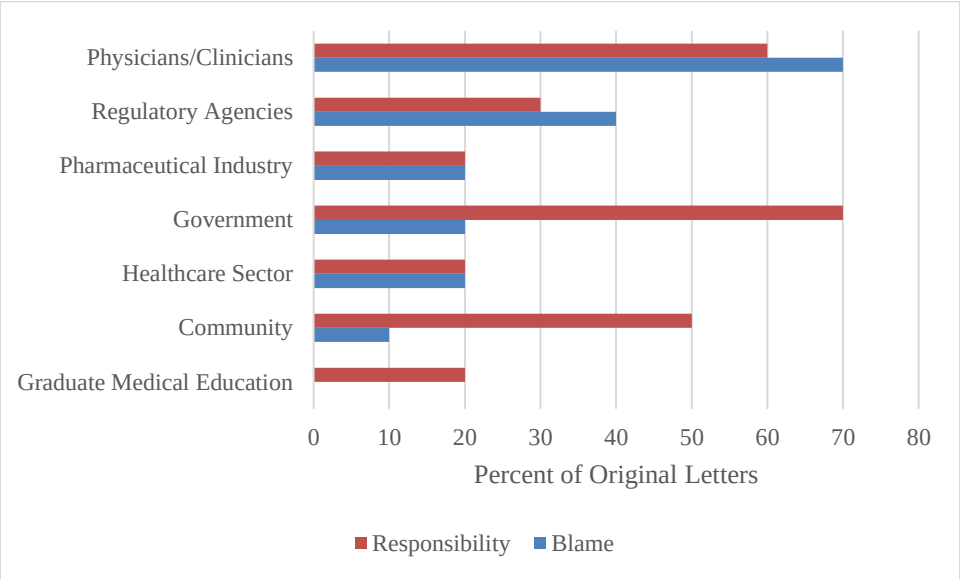

FIGURE 2A. ATTRIBUTIONS OF BLAME AND RESPONSIBILITY AMONG ORIGINAL LETTERS TO THE EDITOR

Research Question 2

Most of the 18 response letters (excluding those by the original authors) disagreed with the original authors (n=9, 50%). An additional 2 (11%) warned about potential unintended consequences. The remainder agreed with the original author but wished to provide additional information, such as describing another study or issue to consider (n=7, 38.9%). Of the 10 original letters, only two received all responses that agreed with the authors. These original letters provided information about PDMPs[29] and described the stigma associated with opioid use disorder and treatment with medications.[61] An additional two letters received responses that warned of potential unintended consequences regarding privacy and PDMPs[34] and the lack of rigorous evidence that naloxone distribution is associated with reduced morbidity and

mortality.[52] Four original articles engendered only responses that were in disagreement, while the remaining three had a mix of responses. The original letters receiving only dissenting opinions were written to argue for more cautious prescribing,[25] review the history of the Joint Commission's role in pain management and opioids[41], defend the FDA's recent actions regarding opioids[44], and provide information about PDMPs.[54] Three of the nine disagreeing letters were solely disagreeing about the original author's interpretation of the evidence in the literature, but not the author's stance, per se. Of the remaining six letters, half were criticizing the Joint Commission and FDA for their roles in the opioid epidemic.[42,45,46] Chhabra (Letter 5, Appendix 2B) concluded, "The Joint Commission did not follow the principles of evidence-based medicine in enacting its pain management guidelines and did little to prevent or decrease opioid use once the epidemic became apparent."[42] Regarding the FDA, Busch (Letter 6, Appendix 2B) said, "I believe the FDA must redirect itself away from its usual criteria and toward actions that can truly make a difference in bringing the opioid epidemic to an end."[46] One article defended the Accreditation Council for Continuing Medical Education's (ACCME) commitment to unbiased continuing medical education, even when funded by the pharmaceutical industry.[58] One response critiqued the approach to reduce opioid prescribing (Letter 1, Appendix 2B), stating, "Patients with severe chronic pain have few options, and some are risky as well".[26] Another response was pessimistic that any efforts by clinicians would deter patients who are addicted to opioids (Letter 4, Appendix 2B), saying "Criminal behavior is something that physicians should be prepared to recognize and deal with effectively to avoid the legal and moral problems associated with prescription drug abuse".[37]

The original authors wrote responses in each case. In 7 of the 11 responses by original authors, the authors maintained their original stance or wrote a neutral response letter. In each of

these cases, their original letters were either “balanced” or neutral. Of the four original letters that were “opioid averse”, three of these authors wrote responses that were either “balanced” or neutral, while one maintained an “opioid averse” tone.

Research Question 3

Figure 2B depicts the positions of all the letters over time. Based on this sample of letters, the early letters tended to be predominantly neutral or “balanced”. Between 2014-2016, the letters were generally fact-based and did not portray any of the positions. After 2016, the discussion turned more toward “opioid averse”. While there was only one “opioid defense” letter, it was early in the time period (2013). Beyond the change in position during the time period, the recommendations in the original letters changed over time. During the 2011-2012 time period, authors were discussing physician-focused action (e.g., PDMPs, clinician training, guidelines, physician education). In 2013-2014, the focus shifted away from physicians (e.g., regulations, access to treatment, development of abuse-deterrent medications). However, this time frame still included discussion of physicians’ role in prescribing as well as stigma. The letters in 2017 focused entirely on recommendations beyond physicians (e.g., supply chain, law enforcement, harm reduction programs, labeling changes, and improving coverage of nonopioid and nonpharmacological treatments). The same colleague who initially reviewed the letters for the major themes reread all of the letters again to assess patterns in the discourse used and changing professional consensus and independently verified my assessment.

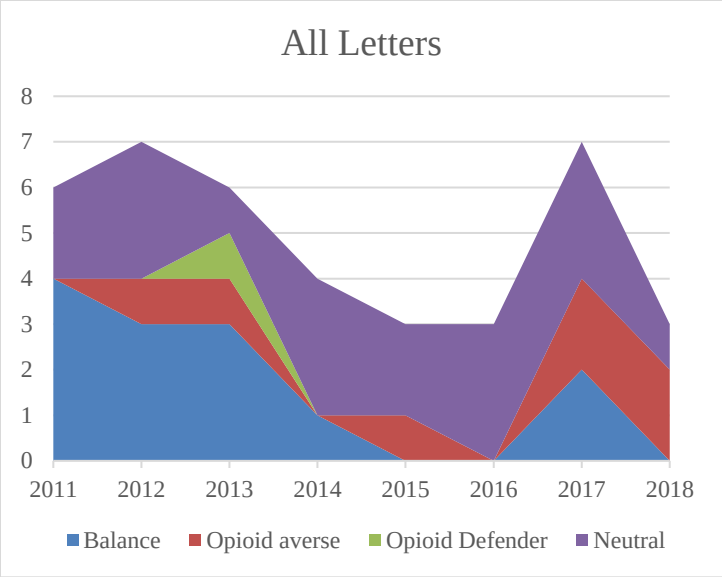

FIGURE 2B. POSITIONS OF LETTERS TO THE EDITOR OVER TIME, ALL LETTERS

Conclusions

A review of letters in *JAMA* between 2011 and 2018 helps summarize the discourse around opioids among the medical community during the peak of the opioid epidemic. The majority of letters were either advocating for a balanced approach between mitigating risk of addiction and appropriately treating pain or neutrally written, to solely provide facts. Therefore, physicians seem to acknowledge the risks associated with opioids, while maintaining that the benefits do outweigh these risks for certain patients or scenarios. Using semi-structured individual interviews with family physicians, Desveaux et al. identified a similar "tension" between providing pain relief and avoiding adverse consequences, including addiction and overdose, and attributed this tension to the physician's identity and role to do what is best for patients.[16] In synthesizing the published qualitative research on the experience of prescribing opioids, Toye et al. identified a similar overarching theme, which she described as "walking a fine line", between the physician's role to relieve pain ("pain is pain") and their professional responsibility to protect society from the opioid epidemic as well as adhere to the new social

norm of limiting opioid prescribing ("social guardianship").[15] These studies included practicing physicians. The parallel conversation playing out in letters to the editor confirms the unique position of physicians within the context of the opioid epidemic. Without additional research, it's unknown whether the letters are a reflection of practicing physicians' collective experiences, or if the letters shaped the social norms of the discipline.

Despite the authors' stance, discourse revolved around describing what led to an increase in opioid deaths ("blame") and strategies to reduce the morbidity and mortality associated with the current opioid crisis ("responsibility"). All original letters included at least one of these themes. Physicians did acknowledge their role in the epidemic, attributing blame to physicians more often than any other group. However, they simultaneously called upon their fellow clinicians and other groups to take steps to mitigate the crisis. Notably, many letters placed responsibility on the government and community. Over time, recommendations moved from changing physician behavior toward policy recommendations. While many TDF domains were present in the letters, the only domain mentioned in over a third of the letters was environmental context and resources, which is consistent with advocacy for other groups to act to change the situation. Prior research has also documented the importance of this domain in the context of opioid prescribing. Desveaux et al. mentioned poor access to mental health/addiction treatment and alternatives to opioids as environmental barriers.[16] Klueh et al. also noted the lack of access to pain specialists as a common challenge falling under environmental context and resources, in addition to barriers such as lack of time.[14] Similarly, Lee et al. identified resources and organizational culture and climate as relevant issues within this domain.[13]

Most letters were in the "neutral" or "balanced" categories, demonstrating a consensus as far as position on the opioid epidemic. While the original articles did include many who were

"opioid averse", most of these authors wrote responses that were "balanced" or "neutral" after reading the responses to their original letters. The lack of "opioid defense" letters is surprising and might be a result of the time period or the journal selected. The one "opioid defense" article was written early in the time period. Over time, the social norm might have sufficiently shifted away from frequent opioid prescribing (as described by Desveaux et al.[16]) such that physicians who disagreed with the letters did not feel comfortable writing a response. The number of "opioid averse" letters did increase at the end of the time period. However, the lack of letters refuting the "opioid averse" letters may indicate a bias by *JAMA.* Journals in the pain and palliative medicine specialties have published editorials claiming the pendulum has swung too far, which may be due to their specialties.[64,65] However, the *New England Journal of Medicine* also published a similar commentary in 2018 warning about unintended consequences of overly restricting opioid prescribing.[66]

Two original letters were written by physicians on behalf of the Joint Commission and the Food and Drug Administration to describe their actions regarding opioids. All letters written in response to these two articles criticized the agencies for downplaying their role in the epidemic and their limited actions taken to mitigate it. The number of times the Joint Commission and FDA were mentioned in the original letters as either causing the epidemic or needing to take steps to address it, combined with the harsh responses to these letters, demonstrates a professional consensus in the medical community that these two agencies created an environment which promoted overprescribing and the subsequent rise in overdose deaths.

Otherwise, much of the disagreement between authors was due to interpretation of the medical literature. For example, responses pointed out that the authors omitted a certain study or failed to adequately present nuanced details about the underlying studies. It seems physicians are

susceptible to confirmation bias, selecting literature to support their beliefs and discounting evidence which does not support their beliefs. The role of identity, social influences, and decision processes on the formation of different beliefs when presented with the same literature would add to the understanding of physician behavior.

The findings from this study are limited to the views of the authors published in *JAMA* during the defined time period. However, describing the viewpoints published in this journal are likely sufficient to adequately describe the views of leaders in the field. However, this approach may present a skewed sample of more academic physicians and fewer community practice physicians. Since this sampling strategy focuses on the physician experience, it might not be generalizable to other healthcare professionals such as nurse practitioners, physician assistants, or nurses.

Future research might analyze letters from a variety of journals across medical specialties to assess any differences across groups, particularly since this study did not find much variation in overall tone. This study also adds to the existing qualitative research from physician interviews, which describe individual opinions or experiences. These letters were not published anonymously and had the goal of shaping physician opinions. However, my results were very similar to those in the scant existing literature. It is clear that physicians recognize their role in both contributing to and solving the opioid crisis, yet they feel the environmental context must also change in order to optimize outcomes. Therefore, rigorous research exploring the effect of interventions across sectors (e.g., government, healthcare, law enforcement) is needed to guide decision making and policy. Finally, research should continue to assess both the outcomes of opioid overdose as well as pain management to ensure the medical community does not lose sight of the “balance” to which they aspire.

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Appendix 2A: Codebook

Code	Definition	Example(s)
Position on Opioid Epidemic		
"Opioid averse"	Authors advocating for limiting the use of opioids, given the consequences of addiction and overdose.	"When risks outweigh benefits, as will often be the case for chronic pain, opioid use should be avoided in favor of other treatments."[35] "Unless clinicians improve prescribing of opiates, more people will become addicted, and the crisis is likely to continue."[34]
"Opioid defense"	Authors warning that a drastic change in opioid prescribing may result in insufficient treatment for and stigma toward chronic pain patients.	"Even though there are risks and benefits of long-term opioid therapy, shifting the focus from opioid-related deaths to limited prescribing of these drugs neither protects patients nor helps clinicians manage patients with chronic pain."[26]
"Balanced"	Authors cautioning that a "balanced" approach between these two extremes is needed.	"A balanced approach to these drugs is needed that minimizes risk though cautious patient selection and safer prescribing, without denying care to those who might benefit."[27] "…it is by well-crafted, multifaceted public health approaches involving prescribers and the public that prescription opioid-related morbidity and mortality can be curtailed while preserving access to medically indicated opioid therapy."[39]
Neutral	Authors presenting simple facts without any text supporting one of the viewpoints above. No text which falls into any of the 3 categories above.	N/A

Appendix 2A Continued: Codebook

Code	Definition	Example(s)
Blame		
Blame – Physicians/Clinicians	Text which explains how an entity or event contributed to the opioid epidemic. Text which focuses on events that happened in the past.	"Signals appeared suggesting that some clinicians had become overzealous in treating pain."[41]
Blame – Regulatory Agencies		"The Joint Commission did not follow evidence-based medicine in enacting its pain management guidelines and did little to prevent or decrease opioid use once the epidemic became apparent."[42]
Blame – Pharmaceutical Industry		"Even though it is well known that prescription opioid use can lead to addiction or overdose, some opioid manufacturers and pain specialists suggest that few patients are susceptible to these risks."[25]
Blame – Government		"Fourth, the criminal justice system often fails to defer to medical judgement in the treatment of opioid use disorders…Physicians working in jails and prisons are seldom allowed to prescribe buprenorphine or methadone."[61]
Blame – Healthcare Sector		"Health care organizations implemented treatment policies and algorithms based on patients' responses to numerical pain scales."[41]
Blame – Community		"….health care practitioners, family members, and the public may attribute the signs and symptoms of these nonopioid disorders to methadone and buprenorphine, adding to the stigma."[61]

Appendix 2A Continued: Codebook

Responsibility		
Responsibility – Physicians/Clinicians	Text which calls for a certain group to take action to address the opioid epidemic. Text which focuses on actions that should happen in the future.	"Reducing inappropriate opioid prescribing will likely have an important role in addressing illicit opioid use."[54]
Responsibility – Regulatory Agencies		"The US Food and Drug Administration (FDA) should revise opioid labels to be consistent with the CDC recommendation."[32]
Responsibility – Pharmaceutical Industry		"Consider removing ultra-high-dosage-unit opioid analgesics from the market."[32]
Responsibility – Government		"Federal funding is needed … because naloxone is an off-patent, generic medication not widely considered to be a promising investment by major pharmaceutical companies."[51]
Responsibility – Healthcare Sector		"Increase insurance coverage of and access to non-opioid and nonpharmacological management of pain."[32]
Responsibility – Community		"Patients and the general public must also become more aware and responsible for the use, storage, and disposal of opioid analgesics, because access to unused left-over medications ahs been reported as the main source for diversion among youth."[36]
Responsibility – Graduate Medical Education		"The first general suggestion is to enhance and update clinical teaching and training practices … in the areas of pain management, opioid pharmacology, and abuse/addiction …"[36]

Appendix 2B: Letters Included In Sample

Unit	Letter	Year	Authors	Specialty	Institution Type	Region	Position
1	Original[25]	2013	Deborah Dowell, MD, MPH; Hillary Kunins, MD, MPH, MS; Thomas Farley, MD, MPH	Internal Medicine Pediatrics	Government Agency	Northeast	Opioid averse
1	Response[26]	2013	Marcin Chwistek, MD	Oncology; Pain	Hospital/Healthcare System	Northeast	Opioid defense
1	Response[27]	2013	Russell Portenoy, MD	Pain	Hospital/Healthcare System	Northeast	Balanced
1	Response by Original Author[28]	2013	Deborah Dowell, MD, MPH; Hillary Kunins, MD, MPH, MS; Thomas Farley, MD, MPH	Internal Medicine Pediatrics	Government Agency	Northeast	Balanced
2	Original[29]	2011	Hallam Gugelmann, MD, MPH; Jeanmarie Perrone, MD	Emergency Medicine	Hospital/Healthcare System	Northeast	Balanced
2	Response[30]	2012	Michael Yokell, ScB; Traci Green, PhD; Josiah Rich, MD	Emergency Medicine; Epidemiology; Infectious Disease	Hospital/Healthcare System	Northeast	Balanced
2	Response by Original Author[31]	2012	Hallam Gugelmann, MD, MPH; Jeanmarie Perrone, MD	Emergency Medicine	Hospital/Healthcare System	Northeast	Balanced
3	Original[32]	2017	Andrew Kolodny, MD Thomas R. Frieden, MD, MPH	Psychiatry; Addiction Medicine; Internal Medicine; Epidemiology	University	Northeast	Opioid averse
3	Response[33]	2018	Mary van den Berg-Wolf, MD	Internal Medicine	Hospital/Healthcare System	Northeast	Opioid averse
3	Response[34]	2018	Elizabeth N. Kinnard, MS; Morgan M. Philbin, PhD, MHS; Leo Beletsky, JD, MPH	Public Health, Law	University	Northeast	Neutral
3	Response by Original Author[35]	2018	Andrew Kolodny, MD Thomas R. Frieden, MD, MPH	Psychiatry; Addiction Medicine; Internal Medicine; Epidemiology	University	Northeast	Opioid averse

Appendix 2B Continued: Letters Included In Sample

Unit	Letter	Year	Authors	Specialty	Institution Type	Region	Position
4	Original[36]	2011	Nora Volkow, MD; Thomas McLellan, PhD	Psychiatry; Psychology	Government Agency	Northeast	Balanced
4	Response[37]	2011	Stella Fitzgibbons, MD	Internal Medicine	Hospital/Healthcare System	Southwest	Neutral
4	Response[38]	2011	Steven Marcus, MD	Emergency Medicine; Pediatrics; Medical Toxicology	Medical School	Northeast	Neutral
4	Response[39]	2011	Perry Fine, MD; Scott Fishman, MD	Anesthesiology	University	West	Balanced
4	Response by Original Author[40]	2011	Nora Volkow, MD; Thomas McLellan, PhD	Psychiatry; Psychology	Government Agency	Northeast	Balanced
5	Original[41]	2017	David Baker, MD, MPH	Internal Medicine	Accrediting Agency	Midwest	Balanced
5	Response[42]	2017	Neeraj Chhabra, MD; Jerrold Leikin, MD	Emergency Medicine	Hospital/Healthcare System	Midwest	Neutral
5	Response by Original Author[43]	2017	David Baker, MD, MPH	Internal Medicine			Balanced
6	Original[44]	2014	Christopher Jones, PharmD, MPH; Peter Lurie, MD, MPH; Janet Woodcock, MD	Public Health, Health Policy, Rheumatology	Government Agency	Northeast	Balanced
6	Response[45]	2015	Jane Ballantyne, MD; Andrew Kolodny, MD	Anesthesiology; Psychiatry	University	Mix	Opioid averse
6	Response[46]	2015	Daniel Busch, MD	Psychiatry	Medical School	Midwest	Neutral
6	Response by Original Author[47]	2015	Christopher Jones, PharmD, MPH; Peter Lurie, MD, MPH; Janet Woodcock, MD	Public Health, Health Policy, Rheumatology	Government Agency	Northeast	Neutral

Appendix 2B Continued: Letters Included In Sample

Unit	Letter	Year	Authors	Specialty	Institution Type	Region	Position
7	Response[48]	2016	William McAuliffe, PhD	Psychiatry	Medical School	Northeast	Neutral
7	Response[49]	2016	Leana Wen, MD, MSc; M. Cooper Lloyd, MD	Emergency Medicine; Internal Medicine; Pediatrics	Government Agency	Mix	Neutral
7	Response by Original Author[50]	2016	Deborah Dowell, MD, MPH; Tamara Haegerich, PhD; Roger Chou, MD	Internal Medicine; psychology	Government Agency	Southeast	Neutral
8	Original[51]	2012	Leo Beletsky, JD, MPH; Josiah Rich, MD, MPH; Alexander Walley, MD, MSc	Public health law; Internal Medicine; HIV/AIDS; Addiction Medicine	Medical School	Mix	Neutral
8	Response[52]	2013	Pamela Leece, MD, MSc; Aaron Orkin, MD, MSc	Family Medicine; Emergency Medicine	University	Canada	Neutral
8	Response by Original Author[53]	2013	Leo Beletsky, JD, MPH; Josiah Rich, MD, MPH; Alexander Walley, MD, MSc	Public health law; Internal Medicine; HIV/AIDS; Addiction Medicine	Medical School	Mix	Balanced
9	Original[54]	2017	Anne Schuchat, MD; Debra Houry, MD, MPH; Gery Guy Jr, PhD, MPH	Internal Medicine; Emergency Medicine; Public Health	Government Agency	Southeast	Opioid averse
9	Response[55]	2017	William Rudman Jr; Peter Corcoran, MPH; Kimberly Elliot, PhD	Public Health; Health Services Research	University	Mix	Neutral
9	Response by Original Author[56]	2017	Anne Schuchat, MD; Debra Houry, MD, MPH; Gery Guy Jr, PhD, MPH	Internal Medicine; Emergency Medicine; Public Health	Government Agency	Southeast	Neutral
10	Original[57]	2012	Lewis Nelson, MD; Jeanmarie Perrone, MD	Emergency Medicine	Medical School	Northeast	Opioid averse
10	Response[58]	2012	Murray Kopelow, MD, MS	Pediatrics	Accrediting Agency	Midwest	Neutral
10	Response[59]	2012	Martin Grabois, MD; Lynn Webster, MD	Physiatry; Pain	Medical School	Mix	Neutral
10	Response by Original Author[60]	2012	Lewis Nelson, MD; Jeanmarie Perrone, MD	Emergency Medicine	Medical School	Northeast	Balanced

Appendix 2B Continued: Letters Included In Sample

Unit	Letter	Year	Authors	Specialty	Institution Type	Region	Position
11	Original[61]	2014	Yngvild Olsen, MD, MPH; Joshua Sharfstein, MD	Internal Medicine; Pediatrics	Government Agency	Northeast	Neutral
11	Response[62]	2014	Jeffrey Stoddard, MD	Pediatrics	Pharmaceutical Company	Northeast	Neutral
11	Response by Original Author[63]	2014	Yngvild Olsen, MD, MPH; Joshua Sharfstein, MD	Internal Medicine; Pediatrics	Government Agency	Northeast	Neutral

Appendix 2C: Matrix of Blame and Responsibility Among Original Letters

	Blame	**Responsibility**
Physicians/ Clinicians	-Increased/over-prescribing (n=8) -Concerns about safety of nonopioid analgesics (n=1) -Prescribing for patient satisfaction scores (n=1) -Pain societies advocating for treating chronic noncancer pain with opioids while minimizing risks (n=1) -Stigma toward patients using medications for treatment of opioid use disorder (n=3)	-Follow or create guidelines/change prescribing (n=2) -Advocacy for prescription drug monitoring programs (n=1) -Co-prescribe naloxone (n=1) -Balance expected benefits and risks of opioids (n=2) -Adopt accurate and nonjudgmental language regarding opioid use disorder and treatment (n=1)
Government	-Increased emphasis on treating pain (Veterans Health Administration (n=1) -Criminal justice system does not support medication-assisted treatment (n=1)	-Increased regulation on prescribing (i.e., mandated PDMP checks) (n=2) -Prescription drug monitoring programs (n=2) -Interstate collaborations for prescription drug monitoring programs (n=1) -Funding for research in overdose prevention (n=1) -Laws to protect clinicians and public prescribing or administering naloxone (n=1) -Standardize legislation and regulation to apply to all opioid medications (n=1) -Expand access to treatment (i.e., criminal justice system, FQHCs) (n=2) -Interrupt supply of illicit opioids, surveillance efforts crossing public health and law enforcement (n=2) -Support harm reduction (e.g., syringes and naloxone) (n=1) -Revise privacy laws to support access to substance use treatment in regular medical record (n=1)
Regulatory Agencies	-Role of Joint Commission mandate (n=3) -FDA continues to approve new opioid medications (n=1)	-FDA: revise existing labeling and limit marketing (n=2) -FDA: approve intranasal naloxone formulations (n=1) -FDA: approve over the counter naloxone (n=1) -FDA: increase supply of naloxone (n=1)
Pharmaceutical Industry	-Reformulation of opioids as extended-release (n=1) -Promote concept that few patients susceptible to addiction or overdose (n=1)	- Unbiased education (for patients and prescribers) (n=1) -Remove high dose opioids from market (n=1)
Graduate Medical Education		-Education regarding pain, opioids, and addiction (n=1) -Training to screen for opioid use and overdose risk (n=1)
Community	-Oppose treatment centers in neighborhood (n=1) -Support groups such as Narcotics Anonymous exclude people using methadone or buprenorphine (n=1) -Language to speak about people with opioid use disorder perpetuates stigma (n=1)	-Be aware of and responsible for safe use, storage, overdose, and disposal (n=3) -Advocacy for prescription drug monitoring programs (n=1) -Harm reduction programs (syringe exchange, first responders trained to administer naloxone) (n=1) -Support broad access to treatment (n=1)

Appendix 2C Continued: Matrix of Blame and Responsibility Among Original Letters

	Blame	**Responsibility**
Healthcare Sector	-Insurers set limits on duration of medications to treat opioid use disorder (n=1) -Disconnect between opioid use disorder treatment and other healthcare (n=1) -Implementation of algorithms for pain medications based on numeric pain rating (n=1)	-Treatment facilities (n=2) -Insurers to cover naloxone and reimburse for overdose prevention education by clinicians (n=1) -Insurers to cover nonopioid and nonpharmaceutical treatments (n=1)

CHAPTER 3: OPIOID PRESCRIBING FOR ACUTE AND POST-SURGICAL MUSCULOSKELETAL PAIN: THE EFFECT OF THE STOP ACT

Introduction

Musculoskeletal injuries, including sprains, strains, and fractures are common, with over 6.8 million injury episodes in the United States annually.[1] Most of these injuries are among people ages 18-64, which has a significant impact on the workforce. Furthermore, pain caused by musculoskeletal injuries and conditions is a common reason for opioid prescribing. Musculoskeletal pain can be either chronic or acute. Since acute musculoskeletal injuries can progress to chronic pain or chronic opioid use, judicious pain management in the acute setting is important.[2,3] Family medicine physicians prescribe the most opioids. While orthopaedic surgeons only represent 2.5% of physicians, they are prescribing 7.7% of prescriptions.[4] Therefore, understanding opioid prescribing among musculoskeletal clinicians is important. Opioids are commonly prescribed to musculoskeletal patients, yet the amount prescribed seems to vary by prescriber and facility characteristics.

In 2018, North Carolina implemented legislation called the Strengthen Opioid Misuse Prevention (STOP) Act. The STOP Act was enacted to decrease the supply of opioids in the community, prevent "doctor shopping", and prevent inappropriate prescribing by requiring clinicians to use available tools and resources.[5] The STOP Act has many provisions, but one is specifically applicable to opioid prescribing for acute and post-surgical pain. Acute pain is defined as pain resulting from any cause which the clinicians expect to last for less than three months. In this case, the STOP Act requires prescribers to prescribe no more than a five-day supply of opioids. If the patient has had a surgical procedure, the prescription cannot exceed seven days.

This study addressed the following research questions: 1) “Was implementation of the STOP Act associated with an increase in the percent of prescriptions written for 7 days or less among patients with acute or post-surgical musculoskeletal conditions?”, and 2) “Which patient, prescriber, and facility characteristics are associated with adherence with STOP Act legislation?”

Review of the Literature

Frequent over-prescribing following orthopaedic surgery has been consistently demonstrated in the literature.[6-11] Over-prescribing can contribute to nonmedical use or diversion through the accumulation of unused pills in the community. Some literature has also documented differences in opioid prescribing by type of hospital, with teaching hospitals prescribing more than community hospitals.[12] Other studies have found residents prescribe higher quantities than attending surgeons or surgeons with more experience.[13-15] Opioid prescribing also varies by gender of the prescriber and geographic region.[15,16]

Several studies assessed factors in general that influence opioid prescribing among musculoskeletal providers. Studies including residents found they commonly report the attending’s preference as the most influential factor influencing their opioid prescribing behavior.[13,17] Other studies identified patient satisfaction and concern that patients will run out of pills as important considerations.[14,17,18] Interestingly, evidence from the literature was not a commonly reported factor influencing prescribing.[17] In a qualitative study, lack of electronic prescribing, issues with coordinating treatment among cross-covering physicians, lack of time to educate patients, and barriers to the use of nonnarcotic pain medications emerged as the predominant barriers to guideline-concordant opioid prescribing among surgeons.[19]

While only ten states had opioid limitation laws in 2016, this type of legislation quickly proliferated, with 39 states having such laws by the end of 2019.[20] A systematic review of studies

assessing the impact of legislation on opioid prescribing found the strength of the evidence to be low. Overall, policies seem to be associated with a reduction in opioid prescribing and overdose, but not a reduction in opioid misuse.[21] Recent research has assessed the influence of state policies focused on a limit on opioid dose,[22,23] mandatory registration for or review of the prescription drug monitoring program,[24,25] mandatory review of opioid use history and signed consent forms for opioid therapy,[26] specific requirements for prescribing lasting more than 3 months,[27] or coprescription of naloxone.[28]

Many states have legislation in effect to restrict the duration or dose of opioid prescriptions. In an analysis of postoperative prescribing in Massachusetts and Connecticut, legislation was associated with a decrease in opioid dose and duration in Massachusetts but not Connecticut. This difference highlights the importance of studying and understanding the local context and multilevel factors which impact prescribing decisions.[29] One study compared New Jersey, where a state prescribing limit and electronic medical record alert were implemented in conjunction, to Pennsylvania as a control and found a 22% greater decrease in opioid dose in New Jersey as compared to Pennsylvania; it is unknown whether the decrease was associated with the legislation or the alert.[30] The New Jersey legislation was associated with a reduction in MME among patients with arthroscopic rotator cuff repair.[31] Florida implemented a duration limit for acute pain; this legislation has been effective at reducing opioid dose and days' supply of opioids, including among orthopaedic surgeons.[32-34]

One study assessed the impact of North Carolina's STOP Act on opioid prescribing at an orthopaedic surgery department at an academic medical center. This study compared the year prior to implementation of the STOP Act to the first year the STOP Act was in effect and included data from 49 prescribers. The authors found a 35% reduction in morphine milligram

equivalents prescribed per prescriber between 2017 and 2018 ($p = 0.0003$).[35] Another study of opioid prescribing after elective orthopaedic surgery at an academic medical center found prescriptions were 3 times as likely to be less than 7 days in 2018 and 3.5 times less likely in 2019 as compared to 2017 (pre-STOP Act). However, these studies are highly susceptible to bias based on other interventions or changes at the same time. Furthermore, one would expect academic medical centers to be the most responsive to new literature and legislation. Finally, both of these studies included elective orthopaedic surgery and postoperative patients. Among orthopaedic trauma patients, trends in opioid dose and duration have been shown to decrease from 2012 to 2017, so studies assessing legislation must account for these baseline trends.[36] No study has assessed the impact of STOP Act on acute musculoskeletal injury, including nonoperative encounters.

The present study addressed these limitations by including prescribers from a large healthcare system of over 12 hospitals and 900 care locations for a broad range of musculoskeletal injuries. It also used an interrupted time series analysis to account for the trend preceding the implementation of the STOP Act. Finally, this study used duration of prescription as the outcome to be consistent with the behavior the legislation targets.

Methods

Study Design

I conducted an interrupted time series analysis to assess trends over time from 2016-2020 and the change in trend associated with implementation of the STOP Act on January 1, 2018, for the percentage of prescriptions written for seven days or less.

I conducted a case control study to assess the association between patient, prescriber, and facility characteristics and prescribing opioids for seven days or less.

Study Population

The target population was patients presenting to a large healthcare system in North Carolina between 2016 and 2020 with a diagnosis of an acute musculoskeletal injury (See Appendix 3A for list of included ICD-10 codes) and the clinicians treating them. In general, I included the ICD-10 diagnosis codes beginning with the letter "S" because they represent injuries. I excluded codes for injuries to internal organs as they are not related to the musculoskeletal system. Similarly, I excluded crushing injuries or traumatic amputations of the head, thorax, and abdomen. I did include crushing injuries and traumatic amputations of extremities. Remaining codes included fractures, sprains, and dislocations.

Inclusion and Exclusion Criteria. For this analysis, I only included facilities located in North Carolina. I included only one encounter for each patient in the analysis. The dataset was first restricted to exclude diagnosis codes for "sequelae" or "subsequent encounters". Then, I selected the first encounter for each patient that *either* had an attending clinician specializing in musculoskeletal care (defined as orthopaedic surgery or sports medicine) or presented to a musculoskeletal specialty clinic to describe the prescribing behaviors of musculoskeletal clinicians. At this point, I excluded encounters at facilities in South Carolina. If records were missing information on duration or duration could not be calculated as described below, I removed them from the study. Finally, prescriptions that were not ultimately ordered due to the clinical decision support intervention were removed (Table 3A).

Data Collection

This healthcare system has collected all opioid and benzodiazepine prescriptions written in its electronic health record since 2015 through a system called Prescription Reporting with Immediate Medication Utilization Mapping (PRIMUM).[37] The PRIMUM Platform includes

several clinical decision support interventions to address controlled substance prescribing; however, no intervention component directly addresses the STOP Act or duration of prescriptions.

The case list of patient encounters for musculoskeletal injuries from 2016-2020 as described above was merged with the PRIMUM database to collect patient risk factors for opioid misuse, prescriber information, and facility information. While PRIMUM collects data on opioids and benzodiazepines, this analysis included only opioid prescriptions.

Variables

Outcome. The main outcome is the duration of opioid prescription. This outcome was dichotomized as either less than or equal to 7 days (i.e., in accordance with STOP Act legislation) or more than 7 days. In some cases, the prescriber did not specify duration in the prescription details. In these cases, I used the prescribed frequency and the prescribed number of pills to calculate the expected duration. For patients who were prescribed multiple opioids at the encounter, if any of the prescriptions was written for more than 7 days, I considered that encounter to be more than 7 days. If all were for 7 days or less, I considered that encounter to be less than 7 days.

Independent Variable. The independent variable was the implementation of STOP Act. This is a time-related variable. Therefore, I considered data prior to January 1, 2018, “pre-STOP Act” and data on or after January 1, 2018, “post-STOP Act”.

Covariates. I included covariates at the patient, prescriber, and facility levels in the hierarchical model. Patient demographics, including gender, race, age, average income of their zip code, diagnosis, and visit type were included as patient-related covariates. The number of opioid prescriptions, the number of encounters the patient had for the indicated injury before

their first musculoskeletal visit, and whether the patient had an inpatient or outpatient orthopaedic surgery were also included. Finally, I included patient risk factors for opioid misuse, as defined by PRIMUM, as patient-related covariates. These factors included: 1) "Early refill" (>50% of previous prescription remaining; 2) 3 or more prescriptions in the past 30 days; 3) two or more onsite administrations of opioids or benzodiazepines in a hospital or emergency department within the past 30 days; 4) history of opioid or benzodiazepine overdose; and 5) history of positive toxicology screen (cocaine, marijuana, or blood alcohol) in the EMR. I included specialty, degree, and whether the attending was a trainee (resident or fellow) as attending-level covariates. Finally, I included the type of facility and whether the facility was a musculoskeletal facility as facility-level covariates.

Data Analysis

Research Question 1. I plotted the percentage of prescriptions written for 7 days or less by month from 2016-2020 as a line graph. I used an interrupted time series analysis to determine if there was a statistically significant change in the percentage of prescriptions written for 7 days or less after implementation of the STOP Act (2018-2020) as compared to pre-STOP Act (2016-2017). In addition, this analysis assessed whether the slope changed between the pre-STOP Act and post-STOP Act time periods. A level change indicates the immediate effect of the STOP Act on duration, while a change in slope indicates a sustained effect over time. Linear regression was used applying the formula below.

$$y = \alpha + \beta_1 T + \beta_2 X + \beta_3 XT + \varepsilon$$

where y=percentage of prescriptions written for 7 days or less (independent variable),

α = intercept,

β = coefficient,

ε = residual (error),

T = time (months numbered sequentially from 1 (January 2016) to 60 (December 2020),

X = study phase (0 = pre-STOP Act, 2016-2017; 1 = post-STOP Act, 2018-2020),

XT = the number of months after implementation of STOP Act

Because chronological data is subject to autocorrelation, I assessed residual autocorrelations to determine the optimal lag order. Newey-West autocorrelation adjusted standard errors with linear regression was used for the final analysis with a lag order of 1.

Research Question 2. I restricted the dataset to the time period after implementation of the STOP Act for this analysis (2018-2020). I excluded records that were missing any variable included in the hierarchical model. Descriptive statistics were used to characterize patient demographics, patient risk factors, prescriber characteristics, and facility characteristics. I compared rates of prescriptions less than or equal to 7 days by patient, prescriber, and facility characteristics using chi-square tests. I also used logistic regression to model the odds of receiving a prescription of 7 days or less at the patient level.

I utilized a three-level hierarchical logistic regression model to predict odds of prescription of 7 days or less, accounting for fixed and random effects at the patient, prescriber, and facility levels. I assessed model fit and selected the most appropriate model for interpretation and application using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values.

Results

Table 3A displays the results of applying the inclusion and exclusion criteria to the dataset. In summary, I included 14,770 prescriptions in the interrupted time series analysis and 6,849 encounters in the hierarchical logistic regression analysis.

TABLE 3A. PATIENT SELECTION

Patient Selection	**Encounters (N)**	**Patients (N)**	**Prescriptions (N)**
Raw Data	332,647	208,265	--
Removed subsequent encounters	304,971	203,904	--
Restricted to patients who presented to MSK clinic/MSK specialty, selected first MSK visit per patient	66,910	41,421	--
Removed patients with first MSK visit in SC	35,204	35,204	--
Restricted to patients prescribed opioid at first MSK visit	12,918	12,918	--
Removed prescriptions not ultimately ordered[a]	12,918	12,918	14,770
Restricted to after STOP Act[b]	6,849	6,849	--

[a]Used for time series analysis
[b]Used for hierarchical logistic regression model

Figure 3A displays the percentage of prescriptions written for seven days or less over time, with the implementation of the STOP Act depicted by a vertical line. The statistical test for white noise determined that these time series data are autocorrelated ($p<0.001$). Figure 3B displays the autocorrelation functions for the time series model. Based on these results, I selected a lag order of 1. Table 3B depicts the final regression model after applying the Newey-West autocorrelation adjusted standard errors with linear regression. The pre-intervention trend was statistically significant before the implementation of STOP Act, with rates of prescriptions for 7 days or less increasing by 1.1% per month (β_1, trend pre-intervention). After controlling for this trend, the level change following implementation of the STOP Act was statistically significant ($p<0.001$), with rates increasing by 17.7% between the pre- and post-intervention periods (β_2, change in level post-intervention). The post-intervention trend differed significantly from the pre-intervention period (β_3, change in trend post-intervention, $p=0.044$). The post-intervention

slope was also significant ($p<0.0001$), with rates continuing to increase by approximately 0.6% per month ($\beta_1 + \beta_3$).

Because the increase also seemed to align with when the STOP Act was signed into law, an identical model was run using that time point, rather than the time point when the STOP Act was implemented (Table 3B). The trend prior to signing of STOP Act is significant, with rates of prescriptions for 7 days or less increasing by 0.6% per month (β_1, trend pre-intervention). After controlling for this trend, the level change following signing of the STOP Act was significant ($p=0.004$), with rates increasing by 15.4% between the pre- and post-intervention periods (β_2, change in level post-intervention). The post-intervention trend did not differ from the pre-intervention period (β_3, change in trend post-intervention, $p=0.101$). The post-intervention slope was significant ($p<0.0001$), with rates continuing to increase by approximately 1.0% per month ($\beta_1 + \beta_3$).

FIGURE 3A. PERCENTAGE OF PRESCRIPTIONS WRITTEN FOR SEVEN DAYS OR LESS OVER TIME

Note: The vertical line indicates when the STOP Act was implemented. The dashed vertical line represents when STOP Act was signed into law.

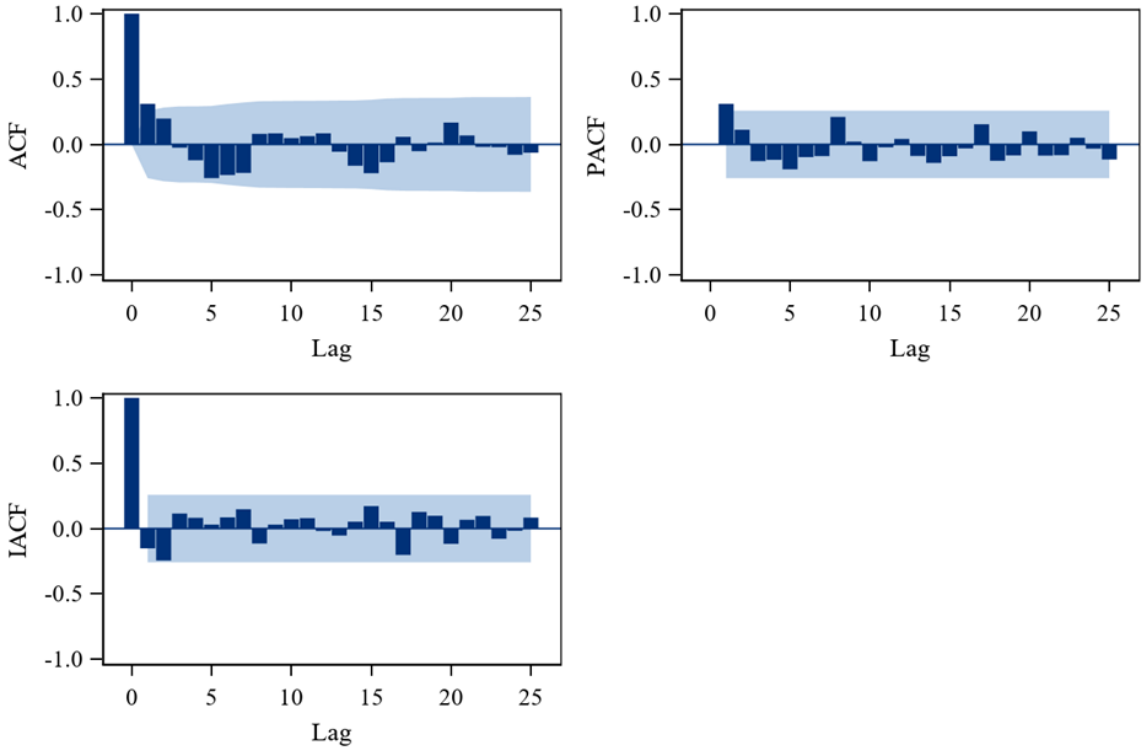

FIGURE 3B. AUTOCORRELATION FUNCTIONS OF THE TIME SERIES MODEL

Table 3C displays the results of the bivariate analysis comparing whether patients were prescribed 7 days or less of opioids by patient, prescriber, and facility characteristics. Overall, 77.1% of encounters included a prescription for 7 days or less. The patient population was 50.5% male, and the majority were between ages 18-64 (72.0%) and White (80.1%). Most patients (61.0%) lived in a zip code where the average income was $25,000-$49,999. The most common PRIMUM risk factor present was early refill (6.8%), and the least common was a history of overdose (0.4%). The knee (37.5%) and shoulder (21.6%) were the most commonly injured body regions, while the abdomen and neck were the least commonly injured (both 0.4%). Sprain was the most common injury (58.1%), and crushing injuries were the least common (1.0%). The majority of encounters were outpatient visits (74.7%). Combined, inpatient and outpatient surgeries represented 72.8% of encounters. Many patients did not have a previous visit for the

injury before presenting to a musculoskeletal (MSK) clinician or facility (79.8%). Most encounters were with an orthopaedic surgery clinician (96.6%), were not with a trainee (99.6%), and were with physicians (97.0%). Most visits were at a hospital (80.0%), and most were not at an MSK-specific facility (84.2%).

TABLE 3B. INTERPRETATION OF REGRESSION COEFFICIENTS, INTERRUPTED TIME SERIES

Parameter	Estimate	Standard Error	p-value	Interpretation
STOP Act Implemented				
β_0	0.218	0.018	<0.0001	Intercept
β_1	0.011	0.002	<0.0001	Trend Pre-STOP Act
β_2	0.177	0.045	0.0002	Change in Level Post-STOP Act
β_3	-0.005	0.002	0.0440	Change in Trend Post-STOP Act
$\beta_1 + \beta_3$	0.006	--	<0.0001	Trend Post-STOP Act
STOP Act Signed into Law				
β_0	0.262	0.015	<0.0001	Intercept
β_1	0.006	0.002	0.0017	Trend Pre-STOP Act Signed
β_2	0.154	0.041	0.0004	Change in Level Post-STOP Act Signed
β_3	0.004	0.002	0.1010	Change in Trend Post-STOP Act Signed
$\beta_1 + \beta_3$	0.010	--	<0.0001	Trend Post-STOP Act Signed

TABLE 3C. BIVARIATE ANALYSES COMPARING WHETHER PATIENTS WERE PRESCRIBED ≤7 DAYS OR >7 DAYS OF OPIOIDS

	Prescription 7 Days or Less N (%) 5277 (77.1%)	**Prescription More than 7 Days N (%) 1572 (23.0%)**	**All Patients N (%)**	**P-value**
Patient Characteristics				
Gender				
Male	2689 (77.8%)	769 (22.2%)	3458 (50.5%)	**0.16**
Female	2588 (49.0%)	803 (23.7%)	3391 (49.5%)	
Age				
<18	336 (79.4%)	87 (20.6%)	423 (6.2%)	**0.09**
18-64	3763 (76.4%)	1165 (23.6%)	4928 (72.0%)	
≥65	1178 (78.6%)	320 (21.4%)	1498 (21.9%)	
Race (n=228 missing)				
Black	874 (77.5%)	254 (22.5%)	1128 (17.0%)	0.72
White	4071 (76.7%)	1234 (23.3%)	5305 (80.1%)	
Other	141 (75.0%)	47 (25.0%)	188 (2.8%)	
Average Income of Patient Zip Code (n=232 missing)				
$25,000-$49,999	3193 (79.2%)	841 (20.9%)	4034 (61.0%)	**<0.0001**
$50,000-$74,999	854 (74.3%)	296 (25.7%)	1150 (17.4%)	
$75,000-$99,999	631 (73.8%)	224 (26.2%)	855 (12.9%)	
$100,000 or more	420 (72.7%)	158 (27.3%)	578 (8.7%)	
PRIMUM Risk Factors*				
Onsite Narcotic Administration	52 (68.4%)	24 (31.6%)	76 (1.1%)	**0.08**
History of Overdose	17 (65.4%)	9 (34.6%)	26 (0.4%)	**0.16**
Positive toxicology	256 (73.4%)	93 (26.7%)	349 (5.1%)	**0.10**
3+ Prescriptions	88 (66.7%)	44 (33.3%)	132 (1.9%)	**0.006**
Early refill	364 (78.6%)	99 (21.4%)	463 (6.8%)	0.42
Body Region*				
Abdomen	18 (69.2%)	8 (30.8%)	26 (0.4%)	0.35
Ankle	997 (79.2%)	262 (20.8%)	1259 (18.4%)	**0.05**
Elbow	444 (81.5%)	101 (18.5%)	545 (8.0%)	**0.01**
Head	44 (86.3%)	7 (13.7%)	51 (0.7%)	**0.13**
Hip	627 (83.7%)	122 (16.3%)	749 (10.9%)	**<0.0001**
Knee	1960 (76.3%)	609 (23.7%)	2569 (37.5%)	0.26
Neck	23 (76.7%)	7 (23.3%)	30 (0.4%)	0.99
Shoulder	1048 (71.0%)	429 (29.1%)	1477 (21.6%)	**<0.0001**
Thorax	92 (77.3%)	27 (22.7%)	119 (1.7%)	0.99
Wrist	231 (89.9%)	26 (10.1%)	257 (3.8%)	**<0.0001**
Injury Type*				
Crushing	62 (88.6%)	8 (11.4%)	70 (1.0%)	**0.02**
Dislocation	714 (78.2%)	199 (21.8%)	913 (13.3%)	0.40
Fracture	1578 (77.5%)	458 (22.5%)	2036 (29.7%)	0.57
Sprain	3027 (76.0%)	955 (24.0%)	3982 (58.1%)	**0.02**
Traumatic Amputation	176 (92.2%)	15 (7.9%)	191 (2.8%)	**<0.0001**
Visit Type				
ED/Urgent Care	457 (81.9%)	101 (18.1%)	558 (8.2%)	**<0.001**
Inpatient	835 (80.8%)	198 (19.2%)	1033 (15.1%)	
Outpatient	3934 (77.0%)	1178 (23.0%)	5112 (74.7%)	
Other	51 (34.9%)	95 (65.1%)	146 (2.1%)	

TABLE 3C CONTINUED. BIVARIATE ANALYSES COMPARING WHETHER PATIENTS WERE PRESCRIBED ≤7 DAYS OR >7 DAYS OF OPIOIDS

Number of Opioid Prescriptions				
One	4763 (78.0%)	1347 (22.1%)	6110 (89.2%)	**<0.0001**
More than one	514 (69.6%)	225 (30.5%)	739 (10.8%)	
Surgery				
No	1303 (70.0%)	558 (30.0%)	1861 (27.2%)	**<0.0001**
Yes, Outpatient	3171 (79.4%)	822 (20.6%)	3993 (58.3%)	
Yes, Inpatient	803 (80.7%)	192 (19.3%)	995 (14.5%)	
Number of Visits for Injury Prior to First MSK Visit				
None	4231 (77.4%)	1234 (22.6%)	5465 (79.8%)	**0.12**
1	914 (76.2%)	285 (23.8%)	1199 (17.5%)	
>1	132 (71.4%)	53 (28.7%)	53 (28.7%)	
Attending Characteristics				
Specialty				
Orthopaedic Surgery	5147 (77.8%)	1467 (22.2%)	6614 (96.6%)	**<0.0001**
Sports Medicine	130 (55.3%)	105 (44.7%)	235 (3.4%)	
Trainee				
Yes	23 (92.0%)	2 (8.0%)	25 (0.4%)	**0.09**
No	5254 (77.0%)	1570 (23.0%)	6824 (99.6%)	
Degree				
MD/DO	5136 (77.3%)	1510 (22.7%)	6646 (97.0%)	**0.01**
PA/NP	141 (69.5%)	62 (30.5%)	203 (3.0%)	
Facility Characteristics				
Type				
Hospital	4291 (78.2%)	1197 (21.8%)	5488 (80.1%)	**<0.0001**
Clinic	986 (72.5%)	375 (27.6%)	1361 (19.9%)	
MSK Site				
Yes	739 (68.4%)	342 (31.6%)	1081 (15.8%)	**<0.0001**
No	4538 (78.7%)	1230 (21.3%)	5768 (84.2%)	

*Not mutually exclusive categories
Bold p-values indicate predictors significant at p<0.2 level

I included the variables that were significant at the p<0.2 level in a logistic regression model presented in Table 3D. Using these same variables, the model building process proceeded as shown in Table 3E. Inclusion of random slopes at the patient-level for each patient-level covariate was too complex of a model; therefore, I fit models including each patient-level covariate as a random slope individually. The only patient level covariate which was statistically significant as a random slope was whether the patient's encounter was for a shoulder diagnosis. Therefore, Model 3 only included shoulder diagnosis as random slope. Shoulder encounter was

only significant at the attending level; therefore, I removed the random slope by facility parameter from subsequent models. Similarly, the attending-level random slopes were not statistically significant in Model 5; therefore, I dropped them from Model 6. In addition, the inclusion of attending-level random slopes in Model 5 did not produce sufficient variation to calculate standard errors, further justifying the exclusion of these parameters from the subsequent model. Based on the AICs in Table 3E, Model 6 was considered the best-fitting model. While the AIC and BIC were slightly higher in Model 6 as compared to Models 4-5, the difference was not substantial. Thus, I selected Model 6 to align with the conceptual model of important covariates at patient, prescriber, and facility levels. Odds ratios and 95% confidence intervals for Model 6 are presented in Table 3F.

TABLE 3D. LOGISTIC REGRESSION, ODDS OF RECEIVING PRESCRIPTION ≤7 DAYS

	OR	**95% CI**
Patient Characteristics		
Gender		
Male	Reference	Reference
Female	0.93	0.83, 1.05
Age		
<18	1.06	0.81, 1.37
18-64	Reference	Reference
≥65	1.14	0.98, 1.32
Average Income of Patient Zip Code (n=232 missing)		
$25,000-$49,999	**1.44**	**1.17, 1.77**
$50,000-$74,999	1.10	0.87, 1.40
$75,000-$99,999	1.05	0.82, 1.34
$100,000 or more	Reference	Reference
PRIMUM Risk Factors*		
Onsite Narcotic Administration	0.61	0.36, 1.02
History of Overdose	0.54	0.23, 1.27
Positive toxicology	0.85	0.65, 1.11
3+ Prescriptions	0.93	0.62, 1.39
Body Region*		
Ankle	**1.22**	**1.02, 1.46**
Elbow	**1.46**	**1.13, 1.90**
Head	1.60	0.70, 3.62
Hip	**1.62**	**1.28, 2.05**
Shoulder	**0.77**	**0.66, 0.91**
Wrist	1.56	0.90, 2.71
Injury Type*		
Crushing	1.86	0.86, 4.01
Sprain	1.01	0.85, 1.19
Traumatic Amputation	**2.33**	**1.17, 4.60**
Visit Type		
ED/Urgent Care	**2.73**	**1.44, 5.15**
Inpatient	**3.33**	**1.15, 9.70**
Outpatient	Reference	Reference
Other	**0.35**	**0.18, 0.68**
Number of Opioid Prescriptions		
One	Reference	Reference
More than one	**0.54**	**0.45, 0.66**
Surgery		
No	Reference	Reference
Yes, Outpatient	**2.36**	**1.31, 4.26**
Yes, Inpatient	0.76	0.31, 1.87
Number of Visits for Injury Prior to First MSK Visit		
None	Reference	Reference
1	0.99	0.84, 1.18
>1	0.77	0.54, 1.09

TABLE 3D CONTINUED. LOGISTIC REGRESSION, ODDS OF RECEIVING PRESCRIPTION ≤7 DAYS

	OR	**95% CI**
Attending Characteristics		
Specialty		
Orthopaedic Surgery	Reference	Reference
Sports Medicine	**0.47**	**0.34, 0.65**
Trainee		
Yes	3.93	0.91, 17.02
No	Reference	Reference
Degree		
MD/DO	Reference	Reference
PA/NP	1.00	0.70, 1.42
Facility Characteristics		
Type		
Hospital	Reference	Reference
Clinic	**2.15**	**1.47, 3.16**
MSK Site		
Yes	Reference	Reference
No	1.28	0.62, 2.61

***Categories are not mutually exclusive. "No" is reference group for each.**

TABLE 3E. ESTIMATES FOR THREE-LEVEL GENERALIZED LINEAR DICHOTOMOUS MODELS OF PRESCRIPTION ≤7 DAYS (N=6,849)

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6** [a]
Model Description	**No predictors, just random effects for intercept**	**Model 1 + Patient level fixed effects**	**Model 2 + random slopes for patient level predictors**	**Model 3 + Attending level fixed effects**	**Model 4 + Random slopes for Attending level predictors**	**Model 5 + Facility Level fixed effect**
Fixed Effects						
Intercept Estimate (standard error)	**1.44 (0.19)**	**1.45 (0.28)**	**1.45 (0.28)**	**1.69 (0.31)**	**1.69 (0)**	**1.63 (0.71)**
Gender						
Male		--	--	--	**--**	--
Female		-0.13 (0.08)	-0.12 (0.08)	-0.13 (0.08)	**-0.13 (0.001)**	-0.13 (0.08)
Age						
<18		0.03 (0.18)	0.05 (0.18)	0.05 (0.18)	**0.05 (0)**	0.05 (0.18)
18-64		--	--	--	**--**	--
≥65		0.01 (0.09)	0.02 (0.10)	0.02 (0.10)	**0.02 (0.003)**	0.02 (0.10)
Average Income of Patient Zip Code						
$25,000-$49,999		0.09 (0.14)	0.10 (0.14)	0.09 (0.14)	**0.09 (0)**	0.09 (0.14)
$50,000-$74,999		-0.0003 (0.15)	0.01 (0.16)	0.01 (0.16)	**0.01 (0.02)**	0.01 (0.16)
$75,000-$99,999		-0.001 (0.16)	0.01 (0.16)	0.005 (0.16)	**0.005 (0)**	0.01 (0.16)
$100,000 or more		--	--	--	**--**	--
PRIMUM Risk Factors*						
Onsite Narcotic Administration		**-0.86 (0.31)**	**-0.86 (0.31)**	**-0.87 (0.31)**	**-0.87 (0)**	**-0.87 (0.31)**
History of Overdose		-0.37 (0.51)	-0.41 (0.51)	-0.42 (0.51)	**-0.42 (0)**	-0.42 (0.51)
Positive toxicology		**-0.32 (0.16)**	-0.31 (0.16)	-0.31 (0.16)	**-0.31 (0)**	-0.31 (0.16)
3+ Prescriptions		-0.11 (0.25)	-0.12 (0.25)	-0.11 (0.25)	**-0.11 (0)**	-0.10 (0.25)
Body Region*						
Ankle		0.01 (0.15)	0.02 (0.15)	0.04 (0.15)	**0.04 (0)**	0.04 (0.15)
Elbow		0.18 (0.17)	0.18 (0.18)	0.17 (0.18)	**0.17 (0)**	0.17 (0.18)
Head		-0.12 (0.49)	-0.13 (0.49)	-0.12 (0.49)	**0.12 (0)**	-0.12 (0.49)
Hip		0.02 (0.17)	0.02 (0.17)	0.01 (0.17)	**0.02 (0.004)**	0.01 (0.17)
Shoulder		**-0.27 (0.11)**	-0.27 (0.14)	**-0.28 (0.14)**	**-0.28 (0)**	**-0.28 (0.14)**
Wrist		0.25 (0.35)	0.26 (0.36)	0.25 (0.36)	**0.25 (0)**	0.26 (0.36)
Injury Type*						
Crushing		0.23 (0.44)	0.20 (0.44)	0.20 (0.44)	**0.20 (0)**	0.20 (0.44)
Sprain		-0.03 (0.11)	-0.05 (0.11)	-0.04 (0.11)	**-0.04 (0)**	-0.05 (0.11)
Traumatic Amputation		0.71 (0.39)	0.73 (0.40)	0.72 (0.40)	**0.72 (0)**	0.72 (0.40)
Visit Type						
ED/Urgent Care		0.38 (0.29)	0.38 (0.29)	0.21 (0.30)	**0.19 (0)**	0.02 (0.44)
Inpatient		-0.33 (0.59)	-0.36 (0.59)	-0.52 (0.60)	**-0.54 (0.001)**	-0.71 (0.68)
Outpatient		--	--	--	**--**	--
Other		0.63 (0.37)	0.65 (0.38)	0.50 (0.38)	**0.49 (0)**	0.33 (0.48)
Number of Opioid Prescriptions						
One		--	--	--	**--**	--
More than one		**-0.74 (0.12)**	**-0.72 (0.12)**	**-0.72 (0.12)**	**-0.72 (0)**	**-0.72 (0.12)**
Surgery						
No		--	--	--	**--**	--
Yes, Outpatient		0.55 (0.26)	0.57 (0.26)	0.39 (0.28)	**0.38 (0)**	0.21 (0.41)
Yes, Inpatient		0.50 (0.53)	0.52 (0.54)	0.51 (0.54)	**0.52 (0)**	0.51 (0.54)
Number of Visits for Injury Prior to First MSK Visit						
None		--	--	--	**--**	--
1		-0.06 (0.10)	-0.05 (0.10)	-0.05 (0.10)	**-0.05 (0)**	-0.05 (0.10)
>1		-0.36 (0.21)	-0.37 (0.21)	-0.39 (0.21)	**-0.39 (0)**	-0.38 (0.21)

TABLE 3E CONTINUED. ESTIMATES FOR THREE-LEVEL GENERALIZED LINEAR DICHOTOMOUS MODELS OF PRESCRIPTION ≤7 DAYS (N=6,849)

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6 [a]**
Model Description	**No predictors, just random effects for intercept**	**Model 1 + Patient level fixed effects**	**Model 2 + random slopes for patient level predictors**	**Model 3 + Attending level fixed effects**	**Model 4 + Random slopes for Attending level predictors**	**Model 5 + Facility Level fixed effect**
Trainee						
Yes				0.89 (1.11)	**0.89 (0)**	0.92 (1.11)
No				--	--	--
Degree						
MD/DO				--	--	--
PA/NP				0.38 (0.45)	**0.40 (0)**	0.44 (0.46)
Facility Type						
Hospital						--
Clinic						-0.05 (0.61)
MSK Site						
Yes						--
No						0.29 (0.74)
Error Variance						
Level-2 (Attending) Intercept	**1.63 (0.28)**	**1.77 (0.30)**	**1.70 (0.31)**	**1.68 (0.30)**	**1.65 (0)**	**1.68 (0.30)**
Level-3 (Facility) Intercept	**0.50 (0.28)**	0.30 (0.21)	0.30 (0.21)	0.22 (0.16)	**0 (0)**	0.22 (0.16)
Random Effects						
$Shoulder_{Attending}$			**0.17 (0.10)**	**0.19 (0.08)**	**0.19 (0)**	**0.19 (0.08)**
$Shoulder_{Site}$			0.01 (0.05)			
$Attending\ Specialty_{Site}$					**0.25 (0)**	
$Trainee_{Site}$					**0 (0)**	
$Attending\ Type_{Site}$					**0 (0)**	
Model Fit						
AIC	5581.76	5360.60	5349.67	5344.89	5344.26	5348.52
BIC	5586.43	5407.26	5399.44	5397.77	5397.14	5404.51

Note: Bold indicates $p<0.05$; $ICC_{Attending} = 0.3011$; $ICC_{Facility} = 0.0923$; Values based on SAS PROC GLIMMIX. Estimation Model = Laplace. Parameter estimates are shown with standard errors in parentheses.

[a]Best fitting model

Overall, the probability of a typical attending at a typical site prescribing an opioid for 7 days or less is 80.8%. Based on the ICC calculations, 30.1% of the variance in prescription duration is accounted for by attending, with another 9.2% accounted for by site. Thus, approximately 61% remains to be accounted for by patient factors. Patients with more than two onsite narcotic administrations within the past 30 days were had 77% lower odds of receiving a prescription for less than 7 days as compared to those without that risk factor (95% CI: 0.23, 0.77). Patients presenting with a shoulder condition had 24% lower odds of receiving a

prescription for less than 7 days as compared to those without a shoulder condition (95% CI: 0.57, 0.995). Patients with more than one opioid prescribed had 62% lower odds of receiving a prescription less than 7 days (95% CI: 0.38, 0.62). Similarly, patients with a sports medicine attending had 66% lower odds of a prescription less than 7 days as compared to those with orthopaedic surgery attendings (95% CI: 0.13, 0.85).

TABLE 3F. ODDS RATIOS FOR THREE-LEVEL GENERALIZED LINEAR DICHOTOMOUS MODELS OF PRESCRIPTION ≤7 DAYS (N=6,849), BASED ON MODEL 6

	OR	**95% CI**
Gender		
Male	--	--
Female	0.88	0.76, 1.03
Age		
<18	1.05	0.68, 1.61
18-64	--	--
≥65	1.02	0.81, 1.29
Average Income of Patient Zip Code		
$25,000-$49,999	1.10	0.75, 1.60
$50,000-$74,999	1.01	0.67, 1.52
$75,000-$99,999	1.01	0.65, 1.55
$100,000 or more	--	--
PRIMUM Risk Factors*		
Onsite Narcotic Administration	**0.42**	**0.23, 0.77**
History of Overdose	0.66	0.24, 1.79
Positive toxicology	0.73	0.54, 1.01
3+ Prescriptions	0.90	0.55, 1.48
Body Region*		
Ankle	1.04	0.78, 1.41
Elbow	1.19	0.84, 1.67
Head	0.89	0.34, 2.32
Hip	1.02	0.73, 1.42
Shoulder	**0.76**	**0.57, 0.995**
Wrist	1.29	0.64, 2.61
Injury Type*		
Crushing	1.22	0.51, 2.92
Sprain	0.96	0.77, 1.18
Traumatic Amputation	2.06	0.94, 4.48

TABLE 3F CONTINUED. ODDS RATIOS FOR THREE-LEVEL GENERALIZED LINEAR DICHOTOMOUS MODELS OF PRESCRIPTION ≤7 DAYS (N=6,849), BASED ON MODEL 6

	OR	95% CI
Visit Type		
ED/Urgent Care	1.02	0.32, 3.23
Inpatient	0.49	0.08, 2.94
Outpatient	--	--
Other	1.38	0.39, 4.87
Number of Opioid Prescriptions		
One	--	--
More than one	**0.49**	**0.38, 0.62**
Surgery		
No	--	--
Yes, Outpatient	1.23	0.46, 3.31
Yes, Inpatient	1.67	0.46, 6.02
Number of Visits for Injury Prior to First MSK Visit		
None	--	--
1	0.95	0.74, 1.21
>1	0.45	0.41, 1.13
Specialty		
Orthopaedic Surgery	--	--
Sports Medicine	**0.34**	**0.13, 0.85**
Trainee		
Yes	--	--
No	2.50	0.28, 21.10
Degree		
MD/DO	--	--
PA/NP	1.56	0.63, 3.83
Facility Type		
Hospital	--	--
Clinic	0.96	0.29, 3.19
MSK Site		
Yes	--	--
No	1.34	0.31, 5.72

Discussion

Overall, the STOP Act had a statistically significant influence on the percentage of prescriptions written for 7 days or less over time. Specifically, there was a 17.7% increase in prescriptions written for 7 days or less after the STOP Act as compared to before ($p<0.001$). This increase was statistically significant even after adjusting for the significant trend which existed

before implementation of STOP Act. Furthermore, rates continued to increase after STOP Act throughout the study period by approximately 0.6% per month. These data also demonstrate a substantial and similar effect when modeling when the STOP Act was signed into law, indicating that clinicians began to change behavior upon the announcement, even up to six months before the legislation would take effect. These results indicate that it may not be necessary to dedicate significant resources into surveillance of physician behavior or enforcement of legislation, at least in this group of clinicians.

There are two studies published on the effect of the STOP Act on musculoskeletal clinicians. Both specifically focused on opioid dosing rather than duration of opioid prescription, which is not consistent with the behavior the legislation targets. However, one study found that an orthopaedic surgery department at an academic medical center had a 35% reduction in dosage between 2017 and 2018.[35] The other did find prescriptions were three times as likely to be for 7-days or less after the legislation.[38] The simple pre-post design did not allow the researchers to isolate the unique impact of the STOP Act in the same way an interrupted time series allows; however, our results are consistent that musculoskeletal clinicians seem to have responded to the legislation. A study assessing the influence of the STOP Act on opioid prescription duration in the emergency department found a 3.3% decrease in opioids prescribed for more than 5 days associated with the STOP Act, which is much lower than the effect identified in the present study, despite controlling for pre-intervention trends.[39] Another study found a decrease in opioid deaths in the year following STOP Act in North Carolina using an interrupted time series design, indicating the legislation had a downstream effect beyond the prescription duration.[40] Finally, an interrupted time series from 2006 to 2018 in North Carolina found that days' supply was not impacted by prior interventions, including the launch of a prescription drug monitoring program

and a state medical board initiative; however, days supply did decrease after the STOP Act legislation.

An interrupted time series analysis of legislation limiting duration of postoperative opioid prescribing in Massachusetts and Connecticut found implementation was associated with a 0.4 day reduction in prescription duration and a 5.9% decrease in the percentage of prescriptions written for more than 7 days in Massachusetts.[29] It seems the 17% change in the proportion of prescriptions adhering to the duration limits in the present study is far larger than the change seen in Massachusetts. The study found no change in Connecticut. However, these were among all postoperative patients and not limited to musculoskeletal pain. It could be that differences among the specific legislation or states account for this difference or that musculoskeletal clinicians are more receptive to the influence of legislation.

After implementation of STOP Act, opioids were prescribed for less than 7 days in 77.1% of encounters. Accounting for the hierarchical nesting of patients, prescribers, and site, the probability of a typical attending at a typical site prescribing an opioid for 7 days or less was 80.8%. A considerable amount of variation existed by attending (30%) and site (9%); however, that left approximately 60% of the variance to be explained by other factors. The model found three patient level covariates associated with statistically significant reduced odds of receiving a prescription for 7 days or less: 1) having 2 or more Emergency Department (ED) or inpatient encounters with onsite narcotic administration within the previous 30 days; 2) having a shoulder injury; and 3) being prescribed more than one opioid. Patients receiving more than one opioid and those that had received opioids at the hospital or ED twice in the month before likely represent patients who have either a more severe injury or other complex medical histories. Interestingly, while shoulder injury was a significant patient-level covariate, the random slope of

shoulder injury by attending was also statistically significant. This finding means that the influence of shoulder injury on the opioid prescription duration differed significantly by attending. It might be that attendings who treat shoulder injuries often have different prescribing practices than those who treat shoulder injuries infrequently. One study in the literature assessed the number of opioid pills consumed by patients following upper-extremity surgical procedures and found that patients undergoing shoulder procedures required the highest number of pills (mean of 22) as compared to patients with wrist, hand, forearm, or elbow procedures.[7] Therefore, my results that shoulder injuries were less likely to result in short prescriptions is consistent with this finding. Still, the study concluded that opioids were being prescribed at rates three times higher than patients needed.

The only attending level covariate which was statistically significant was specialty, with sports medicine clinicians adhering to duration limits less frequently than orthopaedic surgeons. This variation could be due to a difference in training, culture, or patient population. While no study was identified in the literature comparing opioid prescribing between orthopaedic surgeons and sports medicine clinicians, the sports medicine literature documents similar overprescribing of opioids as the orthopaedic surgery literature.[41] Furthermore, one study did find differences in the effect of legislation by specialty.[33]

One limitation of this analysis is using diagnosis codes to identify injuries since some of these diagnoses could have been used for some patients with chronic conditions or sequelae associated with an acute injury. These patients would not be within the scope of the STOP Act legislation. However, the fact that most of the patients in the study did not have a visit for the diagnosis prior to the first visit with an MSK clinician, this patient group likely represents acute injuries. Similarly, I am unable to know for certain that the opioid was prescribed for the

musculoskeletal injury. Limiting to encounters with a musculoskeletal clinician as attending should limit the number of opioids prescribed for other reasons. Another significant limitation is that the prescriber may be a different person from the attending clinician. Attending specialty was the only variable available to restrict the patient group to those presenting to a MSK clinician; however, sometimes the prescriber was a different person than the attending (typically a resident physician or advanced care provider working with the attending). In this analysis, the prescriptions are attributed to the attending, assuming that the attending is the clinician responsible for the care of the patient, including medication prescribing. Finally, while the model identified a significant influence of both attending and site, as well as several important patient, attending, and facility variables, the model could likely be improved by the addition of variable which were not available for this analysis (i.e., patient health insurer, physician demographics, the interaction of physician and patient demographics, and whether the attending was employed by the healthcare organization or by an outside private practice).

The interrupted time series design, correcting for autocorrelation, is a very rigorous design for studying large scale interventions. These data demonstrated a significant increase in percent of prescriptions written for 7 days or less prior to the implementation of STOP Act. Without controlling for that trend, it would be difficult to determine the unique impact of the legislation. Similarly, the multilevel model is a more robust design to determine the influence of patient, prescriber, and facility characteristics on opioid prescribing. The fact that many of the statistically significant associations in the bivariate and logistic regression model were attenuated or no longer significant in the multilevel model demonstrates the necessity for more advanced modeling to account for the nested organization of healthcare delivery. Finally, this study used a large sample of musculoskeletal patients and their clinicians to assess the impact of legislation on

prescriber behavior. These results are likely generalizable to a broad range of musculoskeletal clinicians, at least in the United States.

These results demonstrate significant potential for legislation to effect physician behavior change and potentially patient safety. Future research can build on these results to obtain a richer and more comprehensive understanding of physician behavior in response to legislation. Additional data could be used to enhance the model to obtain a better fit, and interaction terms could be explored to understand how different covariates interact to influence opioid prescribing. These data can be used to identify prescribers who routinely adhere to duration limits (and those that do not) for purposive sampling in a subsequent qualitative study to identify additional targets for intervention. For example, a qualitative study could be designed to understand the uniqueness or complexity of shoulder injuries, based on the findings of this study.

Next steps could also include replicating this study with non-musculoskeletal clinicians to determine whether the impact of legislation is different for other clinicians (i.e., family practice or emergency medicine) treating these same injuries. This study could also be explored for other non-musculoskeletal acute pain conditions, such as headaches. While this study focused on acute injuries, the STOP Act applies to all postoperative patients as well. The impact on prescribing after other orthopaedic procedures, such as total joint replacement, as well as common non-orthopaedic surgical populations, such as cesarean section or cardiovascular procedures, should be assessed. Finally, the impact of STOP Act implementation, and the associated decrease in duration of opioid prescriptions, on patient outcomes, to include chronic opioid use, pain, and community levels of opioid use disorder and overdose, should be assessed to ensure the legislation is having the intended effect.

The results of this study can also be used to guide future legislation and the delegation of resources. Signing the STOP Act into law changed prescriber behavior significantly without additional surveillance or enforcement, before the legislation officially went into effect. Hospitals could also use this information to tailor additional interventions for patient populations or prescribers where adherence to duration limits were lower (i.e., shoulder injury, sport medicine).

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Appendix 3A: Musculoskeletal Conditions and Injuries Included in Study

Diagnosis Code	Description	Parent Category
S02	Fracture of skull and facial bones	Injuries to the head
S03	Dislocation and sprain of joints and ligaments of head	Injuries to the head
S12	fracture of the cervical vertebra and other parts of neck	Injuries to the neck
S13	Dislocation and sprain of joints and ligaments at neck level	Injuries to the neck
S22	Fracture of rib(s), sternum and thoracic spine	Injuries to the thorax
S23	Dislocation and sprain of joints and ligaments of thorax	Injuries to the thorax
S33	Dislocation and sprain of joints and ligaments of lumbar spine and pelvis	Injuries to the abdomen, lower back, lumbar spine, pelvis and external genitals
S42	Fracture of shoulder and upper arm	Injuries to the shoulder and upper arm
S43	Dislocation and sprain of joints and ligaments of shoulder girdle	Injuries to the shoulder and upper arm
S47	Crushing injury of shoulder and upper arm	Injuries to the shoulder and upper arm
S48	Traumatic amputation of shoulder and upper arm	Injuries to the shoulder and upper arm
S52	Fracture of forearm	Injuries to the elbow and forearm
S53	Dislocation and sprain of joints and ligaments of elbow	Injuries to the elbow and forearm
S57	Crushing injury of elbow and forearm	Injuries to the elbow and forearm
S58	Traumatic amputation of elbow and forearm	Injuries to the elbow and forearm
S62	Fracture at wrist and hand level	Injuries to the wrist, hand and fingers
S63	Dislocation and sprain of joints and ligaments at wrist and hand level	Injuries to the wrist, hand and fingers
S67	Crushing injury of wrist, hand and fingers	Injuries to the wrist, hand and fingers
S68	Traumatic amputation of wrist, hand, and fingers	Injuries to the wrist, hand and fingers
S72	Fracture of femur	Injuries to the hip and thigh
S73	Dislocation and sprain of joint and ligaments of hip	Injuries to the hip and thigh
S77	Crushing injury of hip and thigh	Injuries to the hip and thigh
S78	Traumatic amputation of hip and thigh	Injuries to the hip and thigh
S82	Fracture of lower leg, including ankle	Injuries to the knee and lower leg
S83	Dislocation and sprain of joints and ligaments of knee	Injuries to the knee and lower leg
S87	Crushing injury of lower leg	Injuries to the knee and lower leg
S88	Traumatic amputation of lower leg	Injuries to the knee and lower leg
S92	Fracture of foot and toe, except ankle	Injuries to the ankle and foot
S93	Dislocation and sprain of joints and ligaments at ankle, foot and toe level	Injuries to the ankle and foot
S97	Crushing injury of ankle and foot	Injuries to the ankle and foot
S98	Traumatic amputation of ankle and foot	Injuries to the ankle and foot

CHAPTER 4: OPIOID PRESCRIBING FOR CHRONIC MUSCULOSKELETAL CONDITIONS: TRENDS OVER TIME AND IMPLEMENTATION OF SAFE OPIOID PRESCRIBING PRACTICES

Introduction

The opioid epidemic began in the 1990s with a rise in prescription of opioids for pain management.[1] The yearly number of overdose deaths remains at a four-fold increase as compared to 1999.[2] At the same time, millions of Americans suffer from chronic pain, and clinicians face challenges in addressing their pain while optimizing patient safety and minimizing community supply in the context of the drug use and overdose epidemic.[3]

Chronic pain is defined as pain lasting longer than three months or past the time of normal tissue healing. While medical conditions, injuries, or medical procedures can lead to the development of chronic pain, sometimes the cause is unidentifiable.[4] By this definition, approximately 15% of adults have chronic pain, with 11% reporting daily pain.[5,6] Common conditions causing chronic pain are largely musculoskeletal (i.e., arthritis and back or neck problems), although headaches are another common cause.[7] While short-term opioid therapy for noncancer pain lasting less than 12 weeks has demonstrated efficacy, the long-term benefits of opioids for chronic pain are unclear.[8] Because having any prescription for an opioid increases the risk of overdose and opioid use disorder, prescribing these medications without clear evidence of benefit is unwarranted.[9-11] The rate of death from overdose for patients prescribed opioids is 1 in 550. Among those receiving high dose opioids (defined as more than 200 Morphine Milligram Equivalents (MME)), which is common for patients on chronic opioid therapy, the mortality rate is 1 in 32 patients.[12] The rate of overdose also has a positive dose-response relationship, with odds of overdose increasing over 19 MME/day (OR = 1.32), over 50 MME/day (OR = 1.92),

over 100 MME/day (OR = 2.04), and over 200 MME/day (OR=2.88).[13] These rates highlight the importance of guiding clinicians regarding pain management and safe opioid prescribing.

The Centers for Disease Control and Prevention (CDC) released a clinical practice guideline for prescribing opioids for chronic pain in 2016.[14] The CDC guideline provides recommendations regarding 1) determining when it is appropriate to start or continue opioid therapy for chronic pain; 2) selecting the appropriate medication, dose, duration, follow-up, and discontinuation; and 3) evaluating risk for opioid-related harms and mitigating this risk. Appendix 4A lists each of the recommendations included in this guideline. Many healthcare systems have created clinical decision support tools to implement this CPG into clinical practice. Two studies have found that the release of this guideline was associated with a decrease in prescribing rate, high dose prescriptions, co-prescription of opioids and benzodiazepines, days' supply of opioids and lower odds of receiving a high dose opioid nationwide[15,16]; the effect of the guideline on specific groups of prescribers or patients, as well as the influence of simultaneous local, healthcare system-specific interventions, such as policy or clinical decision support interventions is unknown.

Maximizing the utility of the current proliferation of research in both clinical decision support and interventions is critical to influencing opioid prescribing. Identifying strategies that are successful in addition to issues related to the implementation and dissemination of these interventions can guide future research, opportunities for tailoring or targeting interventions, and resource allocation.

This study addressed the following research questions: 1) "Was implementation of a clinical decision support intervention associated with a decrease in the percent of chronic musculoskeletal pain patients receiving opioid prescriptions and/or opioid dose?", and 2) "Which

prescriber and facility characteristics are associated with adherence with safe opioid prescribing practices in response to a clinical decision support intervention?"

Review of the Literature

Clinical Decision Support

Researchers, clinicians, and healthcare administrators are developing, implementing, and testing interventions to reduce inappropriate prescribing. Clinical informatics system strategies are an important focus area as electronic health records reach saturation. Healthcare systems have implemented and evaluated a variety of electronic interventions, including power plans/order sets,[17-19] dashboards,[20-22] risk assessment/screening,[23-25] alerts,[26-28] changes to default prescription details[29-31], integration of PDMP within the EMR[32], and other decision support.[22,33,34] Many studies of clinical decision support interventions for opioid prescribing focus on patients in the emergency department (ED)[19,25-28,31], while others are broadly implemented in large healthcare systems[21,22] or specific specialties.[17,18,34] Most studies found the interventions to be effective[20-23,25,26,33,34] or had mixed results[29,30,32], having an effect on some outcomes but not all.[17,18,24,27,28]

Alerts were first used to reduce adverse drug events by warning of contraindications or allergies to medications.[35-37] Since then, healthcare teams have used alerts to address varied clinical decisions, including opioid prescribing. Gugelmann et al. created an alert that "popped up" at the time of prescribing to alert the prescriber to screen for the following risk factors: psychiatric illness, chronic pain, substance abuse, and age younger than 65.[26] The alert also prompted the prescriber to consider non-opioid medications and non-pharmaceutical remedies. The alert did result in statistically significant decreased opioid prescribing, but this alert triggered for every opioid prescription rather than just for patients meeting the risk factors, which could contribute to "alert fatigue". Other alerts only trigger for patients meeting defined criteria. For

example, an alert in the emergency department setting informs other ED prescribers that the patient had either 1) already been referred to an outpatient pain management program[27] or 2) had an existing Opioid Care Plan on record.[28] Results were mixed for these studies, but did have a statistically significant effect on MME prescribed,[28] number of prescriptions filled,[27] and number of prescribers per patient.[27] However, no study has assessed the effectiveness of alerts for opioid prescribing among patients with musculoskeletal conditions specifically; nor have researchers rigorously attempted to determine the specific patient, clinician, and/or healthcare facility characteristics that affect response to and efficacy of clinical decision support interventions such as alerts.

Opioid Dosage

The risk of opioid use disorder and overdose increases with opioid dosage, while pain typically does not improve at higher doses.[38] Opioid dose is typically measured using morphine milligram equivalents (MME) to allow for direct comparison of dose across different opioid medications. One study found 6.1% of patients with high dose chronic therapy (defined as $\geq$120 MME/day) opioid abuse or dependence as compared to only 0.7% among patients with lower doses ($\leq$36 MME).[9] Two studies have found a dose-response relationship between opioid dose and overdose rate, with risk of death increasing by 32% for patients receiving 20-49 MME/day and increasing as much as 288% for patients receiving $\geq$200 MME/day.[13,39] While no clear threshold delineates a point at which the risk of adverse outcomes is eliminated, the CDC Guideline advocates for prescribers to use caution for doses exceeding 50 MME/day and to avoid exceeding 90 MME/day.[14]

Naloxone

Naloxone is a medication that can reverse respiratory depression and overdose associated with opioid use. The efficacy of prescribing naloxone on overdose death rates is not well studied; however, experts agree that prescribing naloxone when patients have risk factors that increase their chance of overdose is justified.[14] The CDC Guideline suggests prescribing naloxone to patients with a history of overdose, a history of substance use disorder, opioid dose exceeding 50 MME/day, or concurrent benzodiazepine use.[14]

Risk Mitigation and Pain Agreements

Checking prescription drug monitoring programs (PDMPs), using urine drug testing, and implementing pain agreements are common techniques promoted to decrease the risk of adverse outcomes associated with opioids. However, clinicians do not commonly use pain agreements, and their efficacy is not well-studied.[40-43] One systematic review of 11 studies found most studies assessing the effectiveness of pain agreements was low quality evidence. Of the higher-quality studies, treatment agreements were associated with a 7-23% reduction in opioid misuse.[44] The CDC Guideline, therefore, does not specifically recommend their use. The guideline does recommend establishing treatment goals, discussing risks and benefits of opioids, and the patient and clinician responsibilities for managing therapy.[14] These activities may be operationalized and standardized through a pain agreement.

Co-Prescribed Sedating Medications

The CDC Guideline recommends avoiding co-prescribing opioids and benzodiazepines because they both can decrease respiration as central nervous system depressants.[14] Use of both of these medications concurrently increases the risk of overdose. One study found the risk of overdose death increased four times for patients on opioid therapy with a concurrent

benzodiazepine prescription.[45] Management of patients requiring both of these medications is complex and should involve pharmacists and/or pain specialists to ensure patient safety.

Extended Release Opioids

The U.S. Food and Drug Administration has warned of serious risks associated with extended release opioids (i.e., methadone, transdermal fentanyl, and extended-release oxycode). The label for these medications recommends they only be used for pain requiring around-the-clock opioids and when other treatments (e.g., nonopioid analgesics or immediate-release opioids) are ineffective.[46] The CDC Guideline, therefore, recommends that patients initiating opioid therapy begin with an immediate-release opioid.[14]

Pain Management for Chronic Musculoskeletal Pain

Musculoskeletal diseases affect approximately half of U.S. adults and up to three-quarters of U.S. adults over the age of 64.[3] Worldwide, low back pain is the leading cause of disability, contributing to the global burden of disease with 57.6 million years lived with disability.[47] Musculoskeletal disorders overall (e.g., rheumatoid arthritis, osteoarthritis, low back pain, neck pain, gout) contribute significantly to the burden of disease. Globally, 1.3 billion people are living with one of these conditions, contributing to 138 million years lived with disability. This prevalence outnumbers all communicable, maternal, neonatal, and nutritional disorders, and injuries combined. Musculoskeletal conditions are responsible for over 20% of years lived with disability of all noncommunicable diseases, outnumbering the burden from cancer, cardiovascular disease, chronic respiratory diseases, liver diseases, digestive diseases, neurological disorders, and diabetes/endocrine diseases. Only mental and substance use disorders have a similar impact on the health of the global population, affecting 1.1 billion and contributing to 150 million years lived with disability. Globally, back pain is the leading cause of

years lived with disability, while neck pain and other musculoskeletal conditions are also in the top ten. Among high income countries, back pain, neck pain, other musculoskeletal conditions, and osteoarthritis are in the top ten. At the same time, opioids are the eighth leading cause of years lived with disability in the United States. Therefore, clinicians are faced with a large population of patients suffering from chronic pain associated with musculoskeletal conditions and a simultaneous epidemic of opioid use disorder.

The literature, however, does not support significant improvement in pain or function among patients with osteoarthritis on chronic opioid therapy as compared to nonopioid analgesics.[48] In 2017, the American Academy of Orthopaedic Surgeons (AAOS) released a clinical practice guideline recommending against the use of opioid analgesics to treat osteoarthritis.[49] Another AAOS guideline on nonsurgical management of osteoarthritis promotes low-impact exercise but not opioid medications.[50] Still, one study found that approximately 27% of encounters for patients with osteoarthritis in a large healthcare system were prescribed an opioid.[51] While opioids may have short term efficacy for chronic back pain, the long-term effectiveness and the impact on function are unknown and complicated by drug tolerance and hyperalgesia.[52] No trials have exceeded four months, and most have high dropout rates. A recent systematic review for opioids for back pain found opioids may provide pain relief for 4-15 weeks, as no studies exceeded 15 weeks of follow-up.[53] This same review found no reduction in disability compared to placebo. One study found internal medicine physicians who scored higher on board examinations were less likely to prescribe opioids for back pain as compared to those with lower scores.[54]

While the benefits of chronic opioid therapy in these patient populations are unclear, adverse effects include dependence on opioids after arthroplasty, inadequate analgesia following

arthroplasty, poor surgical outcomes, hypogonadism, androgen insufficiency, constipation, and decreased pain tolerance.[55-62]

This study adds to the literature by using rigorous study designs to determine the impact of a clinical decision support tool designed to improve adherence to the CDC Guideline as well as quantifying physician compliance with the guideline using a novel measure. Furthermore, it assesses the influence of prescriber and facility factors on guideline concordant physician behavior.

Methods

Study Design

I conducted an interrupted time series analysis to assess trends over time from 2016-2020 and the change in trend associated with the implementation of a clinical decision support toolkit to operationalize the CDC Guideline for prescribing opioids for chronic pain in October of 2017 for the percentage of patients receiving an opioid and the average opioid dose for patients who do receive an opioid.

I conducted a case control study to assess the association between prescriber and facility characteristics and safe opioid prescribing practices, including: 1) prescribing naloxone for patients at high risk; 2) initiating a pain agreement for patients on chronic opioid therapy; 3) prescribing < 90 MMEs; 4) cancelling an extended release opioid for an opioid naïve patient; and 5) avoiding co-prescribed sedative medications.

Study Population

The target population was patients presenting to a large healthcare system between 2016 and 2020 with a diagnosis of a chronic musculoskeletal condition (See Appendix 4B for a list of included ICD-10 codes) and the clinicians treating them. I included arthropathies, to include inflammatory arthropathy and degenerative arthropathy (osteoarthristis), as well as chronic

conditions of the spine, to include deforming dorsopathies, spondylopathies, and other dorsopathies. I chose these diagnoses because they are common, chronic, and painful musculoskeletal conditions in which the evidence for efficacy of long-term opioid therapy is lacking.

Inclusion/Exclusion Criteria. For this analysis, I removed records which were missing facility name. To exclude postoperative prescriptions, this analysis was limited to encounters in the ambulatory setting. Furthermore, once a patient had an inpatient visit with an orthopaedic surgery attending, I removed subsequent ambulatory visits for that patient. I did this to limit the focus to patients with the condition who had not received an operation to attempt to improve the condition. For example, including patients with osteoarthritis after joint replacement would underestimate opioid prescribing as many patients no longer require opioids after joint replacement. I also chose to limit to the ambulatory setting to capture clinicians employed by the healthcare system. Including inpatient or emergency department visits might capture patients who then follow up at practices outside of the healthcare system, which would also underestimate opioid prescribing as the database would not capture any opioids they received outside the healthcare system. I removed encounters at urgent care locations as well as encounters at an oncology clinic or with an oncology clinician.

To assess opioid dosage, I limited to encounters with an opioid prescription completed and removed records which were missing information necessary to calculate MME.

Data Collection

This healthcare system has collected all opioid and benzodiazepine prescriptions written in their electronic medical record (EMR) since 2015 through a system called Prescription Reporting with Immediate Medication Utilization Mapping (PRIMUM).[63] The PRIMUM

Platform includes several clinical decision support interventions to address controlled substance prescribing and operationalize the CDC Guideline for Chronic Pain (Appendix 4A). Related to this study, PRIMUM included the following five interventions:

Original PRIMUM alert: This alert notifies the prescriber in real time of the presence of potential risk factors for abuse, misuse, and diversion of prescription opioids. The PRIMUM alert includes eight patient risk factors: 1) "Early refill" (>50% of previous prescription remaining); 2) 3 or more prescriptions in the past 30 days; 3) two or more onsite administrations of opioids or benzodiazepines in a hospital or emergency department within the past 30 days; 4) history of opioid or benzodiazepine overdose; 5) history of positive toxicology screen (cocaine, marijuana, or blood alcohol) in the EMR; 6) initiating an opioid prescription for a patient with a current benzodiazepine prescription; and 7) initiating a benzodiazepine prescription for a patient with a current opioid prescription. Prescribers have the option to cancel the prescription, proceed with the current prescription, or make changes based on the alert. See Figure 4C.1 for an example of this alert.

Extended Release alert: This alert triggers when a prescriber initiates an extended-release opioid for an opioid naïve patient (Figure 4C.2). Prescribers can either continue or cancel the prescription.

Pain Agreement alert: This alert suggests completion of a standardized pain agreement for patients who have exceeded 90 days of continuous opioid therapy (Figure 4C.3). Prescribers can either click to launch the pain agreement or continue without starting a pain agreement.

Naloxone alert: This alert suggests a naloxone prescription for patients at high risk of overdose, including patients receiving high dose opioids (greater than 50 morphine milligram equivalent), receiving concurrent benzodiazepine and opioid prescriptions, or with a history of opioid or benzodiazepine overdose (Figure 4C.4).

Controlled Substance Review Component: A page in the EMR was created to display all controlled substance information, including prescriptions and on-site administrations, as well as all risk factors in the PRIMUM alert "on demand". This means a prescriber can proactively access this page before initiating a prescription. In addition, this page displays the patient's opioid dose in MME. If the patient has an MME greater than or equal to 90, the text displays in red, indicating high risk.

The case list of patient encounters for musculoskeletal conditions from 2016-2020 as described above was linked to the PRIMUM database to collect prescriber information, prescription information, and prescriber response to each alert. While PRIMUM collects data on opioids and benzodiazepines, I limited my analysis to opioid prescriptions.

Variables

Outcome. The main outcome is safe opioid prescribing practices. This outcome is a composite score of the frequency at which a prescriber does the following behaviors in response to the clinical decision support intervention: 1) cancels a prescription when alerted that he/she is going to prescribe an opioid when the patient is already prescribed a benzodiazepine; 2) initiates a pain agreement when prompted that a patient has reached over 90 days of continuous opioid therapy; 3) prescribes naloxone when alerted that the patient is at high risk for overdose; 4) cancels a prescription for an extended release opioid when alerted that patient is opioid naïve; and 5) prescribes opioids less than 90 MME. A weighted percentage will be calculated,

according to the formula below, to obtain the composite score, which will be a percentage ranging from 0 to 100. The score will be calculated for each unique prescriber.

$$\frac{(E_{coprescribe}*p_{cancelled})+(E_{90\ day}*p_{agreement})+(E_{high\ risk}*p_{naloxone})+(E_{ER}*p_{cancelled})+(N_{rx}*p_{\leq 90MME})}{(E_{coprescribe}+E_{90\ day}+E_{high\ risk}+E_{ER}+N_{rx})}$$

where $E_{coprescribe}$ is the number of encounters in which the prescriber received the coprescription alert and $p_{cancelled}$ is the proportion of those encounters in which the prescriber cancelled the prescription,

where $E_{90\ day}$ is the number of encounters in which the prescriber received the 90-day alert and $p_{agreement}$ is the proportion of those encounters in which the prescriber initiated a pain agreement,

where $E_{high\ risk}$ is the number of encounters in which the prescriber received the high risk of overdose alert and $p_{naloxone}$ is the proportion of those encounters in which the prescriber prescribed naloxone,

where E_{ER} is the number of encounters in which the prescriber received the extended release alert and $p_{cancelled}$ is the proportion of those encounters in which the prescriber cancelled the extended release opioid,

where N_{rx} is the number of opioid prescriptions written by the prescriber and $p_{\leq 90MME}$ is the proportion of those prescriptions that are less than or equal to 90 MME.

I chose this weighted average because, while all of these behaviors are recommended by clinical practice guidelines, not all apply to every opioid prescribing encounter. For example, only some patients are eligible for pain agreements or naloxone. Some prescribers may only get these alerts a few times despite prescribing opioids often. The weighting prevents a small number of

encounters in any one category from leading to an over- or under-representation of the prescriber's overall opioid safety behavior.

Independent Variable. The independent variable is implementation of the clinical decision support toolkit in October of 2017. This is a time-related variable, therefore, I considered data prior to October 2017 "pre-implementation" and data on or after October 2017 "post-implementation".

Covariates. I included covariates at the prescriber and facility levels in the hierarchical model. The number of patients prescribed an opioid, the number of opioid prescribing encounters, specialty and type of prescriber were included as prescriber-level covariates. In addition, I summed up the following patient-level variables to the prescriber level to provide an indication of case mix: diagnosis, gender, age, race. For example, the percent of female patients was calculated for each prescriber. Finally, I included the type of facility (large practice with many different clinics vs. Single clinics) and whether the facility specialized in musculoskeletal conditions of interest (defined as orthopaedic surgery, neurosurgery, or rheumatology) as facility-level covariates.

Data Analysis

Research Question 1. I plotted the rate of opioid prescribing by month from 2016-2020 as a line graph. I applied the same methodology for average MME of opioid prescriptions over the same time period.

I used an interrupted time series analysis to determine if the percentage receiving an opioid prescription or the average MME after implementation of the clinical decision support interventions (October 2017-December 2020) experienced a statistically significant change as compared to baseline (January 2016-September 2017). In addition, this analysis assessed

whether the slope changed between the baseline intervention time periods. A level change indicates immediate effect of the intervention on opioid prescribing and/or dosage, while a change in slope indicates a sustained effect over time. Linear regression was used applying the formula below.

$$y = \alpha + \beta_1 T + \beta_2 X + \beta_3 XT + \varepsilon$$

where y=percentage of patients receiving an opioid prescription OR average MME of opioid prescriptions;

α = intercept,

β = coefficient,

ε = residual (error),

T = time (months numbered sequentially from 1 (January 2016) to 60 (December 2020),

X = study phase (0 = baseline, January 2016-September 2017; 1 = intervention, October 2018-December 2020),

XT = the number of months after implementation of intervention

Because chronological data is subject to autocorrelation, I assessed residual autocorrelations to determine the optimal lag order. Newey-West autocorrelation adjusted standard errors with linear regression was used for the final analysis with a lag order of 1.

Research Question 2. I included all encounters for the population described above in which an opioid prescription was initiated between October 2017 and December 2020. I removed prescribers who prescribed an opioid to less than 10 patients during the study period. For prescribers who practice at multiple locations, I assigned them to the practice from which they wrote the most prescriptions. In one case, a prescriber wrote equal number of prescriptions from multiple sites; I selected the first site alphabetically. Descriptive statistics were used to

characterize prescriber characteristics and facility characteristics. I compared median composite safe opioid prescribing score by prescriber and facility characteristics using Kruskal--Wallis H tests for categorical variables and Spearman's rho for continuous variables. I also used a multiple linear regression model to predict safe opioid prescribing score. I utilized a two-level hierarchical linear regression model to predict safe opioid prescribing, accounting for fixed and random effects at the prescriber and facility levels. I assessed model fit and selected the most appropriate model for interpretation and application using AIC and BIC values.

Results

Table 4A displays the results of applying the inclusion and exclusion criteria to the dataset. In summary, I included 1,289,697 encounters in the time series assessing whether an opioid is prescribed, 154,299 encounters in the time series assessing MME, and 606 prescribers in the hierarchical linear regression analysis.

Figure 4A displays the percentage of encounters resulting in an opioid prescription, with the implementation of the clinical decision support intervention depicted by a vertical line. The statistical test for white noise determined that these time series data are autocorrelated ($p<0.001$). Figure 4B displays the autocorrelation functions for the time series model. Based on these results, I selected a lag order of 1. Table 4B depicts the final regression model after applying the Newey-West autocorrelation adjusted standard errors with linear regression. The pre-intervention trend was statistically significant before the implementation of clinical decision support intervention, with rates of opioid prescriptions decreasing by 0.2% per month (β_1, trend pre-intervention). After controlling for this trend, the level change following implementation of the intervention was statistically significant ($p<0.001$), with rates decreasing by 1.6% between the pre- and post-intervention periods (β_2, level change post-intervention). The post-intervention trend differed significantly from the pre-intervention period (β_3, change in trend post-

intervention, p=0.044). The post-intervention slope was also significant (p<0.0001), with rates continuing to decrease by approximately 0.1% per month ($\beta_1 + \beta_3$).

TABLE 4A. PRESCRIBER SELECTION

Step	Encounters	Patients	Prescribers
Raw Data	2,990,836	692,435	--
Removed records with missing site	2,987,863	690,423	--
Remove encounters for patients that happened AFTER a inpatient visit with ortho attending OR any visit to a hospital with ortho attending (assuming that's a surgery)	2,767,574	669,792	--
Limited to Ambulatory	1,368,613	412,073	--
Removed Urgent Care	1,290,746	370,183	--
Removed cancer (by specialty and location) [a]	1,289,697	369,877	--
Limited to Encounters with completed Opioid Prescription	154,417	62,419	--
Removed missing MME[b]	154,299	62,375	--
Expanded to add encounters with opioid initiated	155,703	62,692	--
Limit to October 2017-December 2020	81,867	36,634	1,368
Limit to prescribers with at least 10 opioid patients[c]	--	--	606

[a]Used for time series analysis with outcome of whether patient was prescribed an opioid
[b]Used for time series analysis with outcome of MME
[c]Used for multilevel model

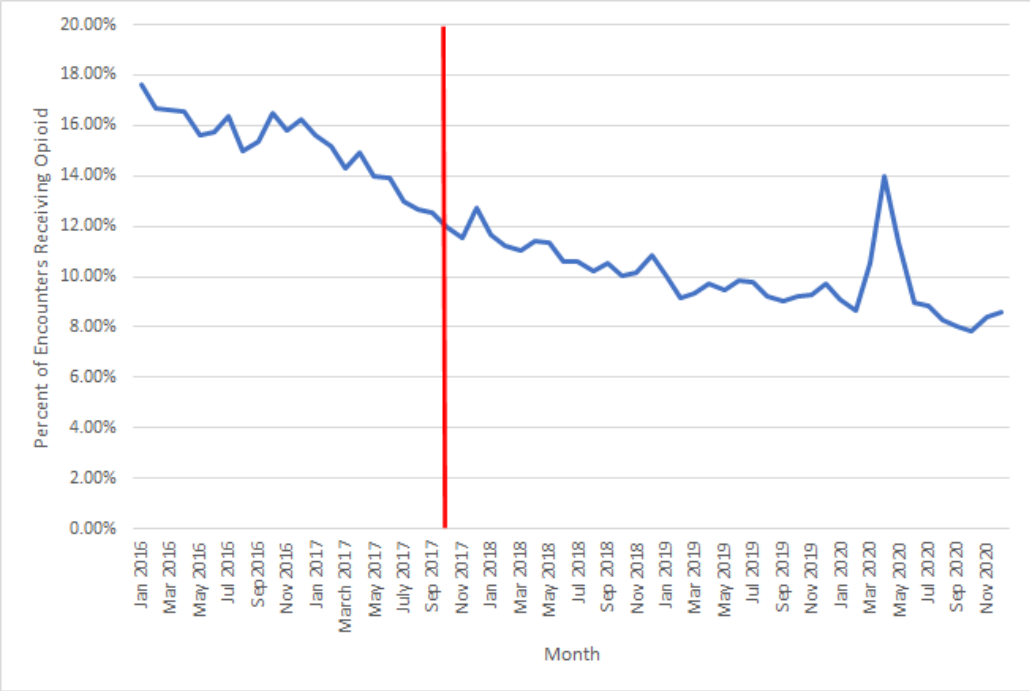

FIGURE 4A. PERCENTAGE OF ENCOUNTERS RESULTING IN OPIOID PRESCRIPTION OVER TIME

Note: The vertical line indicates when the clinical decision support intervention was implemented.

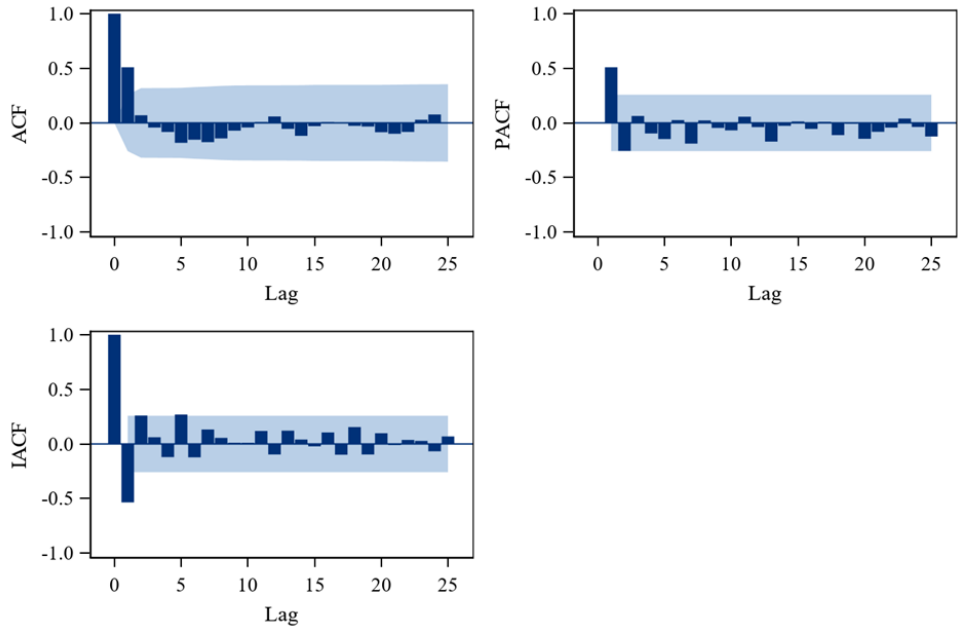

FIGURE 4B. AUTOCORRELATION FUNCTIONS OF THE TIME SERIES MODELING PERCENT OF ENCOUNTERS RESULTING IN OPIOID PRESCRIPTION

TABLE 4B. INTERPRETATION OF REGRESSION COEFFICIENTS, INTERRUPTED TIME SERIES, ENCOUNTERS RESULTING IN OPIOID PRESCRIPTION

Parameter	Estimate	Standard Error	p-value	Interpretation
β_0	0.175	0.003	<0.0001	Intercept
β_1	-0.002	0.000	<0.0001	Trend Pre-Intervention
β_2	-0.016	0.004	0.0002	Change in Level Post-Intervention
β_3	0.001	0.000	<0.0001	Change in Trend Post-Intervention
$\beta_1 + \beta_3$	-0.001	--	<0.0001	Trend Post-Intervention

Figure 4C displays the average MME of opioid prescriptions over time, with the implementation of the clinical decision support intervention depicted by a vertical line. The statistical test for white noise determined that these time series data are autocorrelated ($p<0.001$). Figure 4D displays the autocorrelation functions for the time series model. Based on these results, I selected a lag order of 1. Table 4C depicts the final regression model after applying the Newey-West autocorrelation adjusted standard errors with linear regression. The pre-intervention trend was not statistically significant before the implementation of clinical decision support intervention, with average MME decreasing by less than 1 MME per month (b1). The level change following implementation of the intervention was not statistically significant either ($p<0.001$), with average MME increasing by less than 1 MME between the pre- and post-intervention periods. The post-intervention trend did not differ significantly from the pre-intervention period (b3, $p=0.279$). The post-intervention slope was significant ($p<0.0001$), with rates continuing to decrease by 0.16 MME per month (b1+b3).

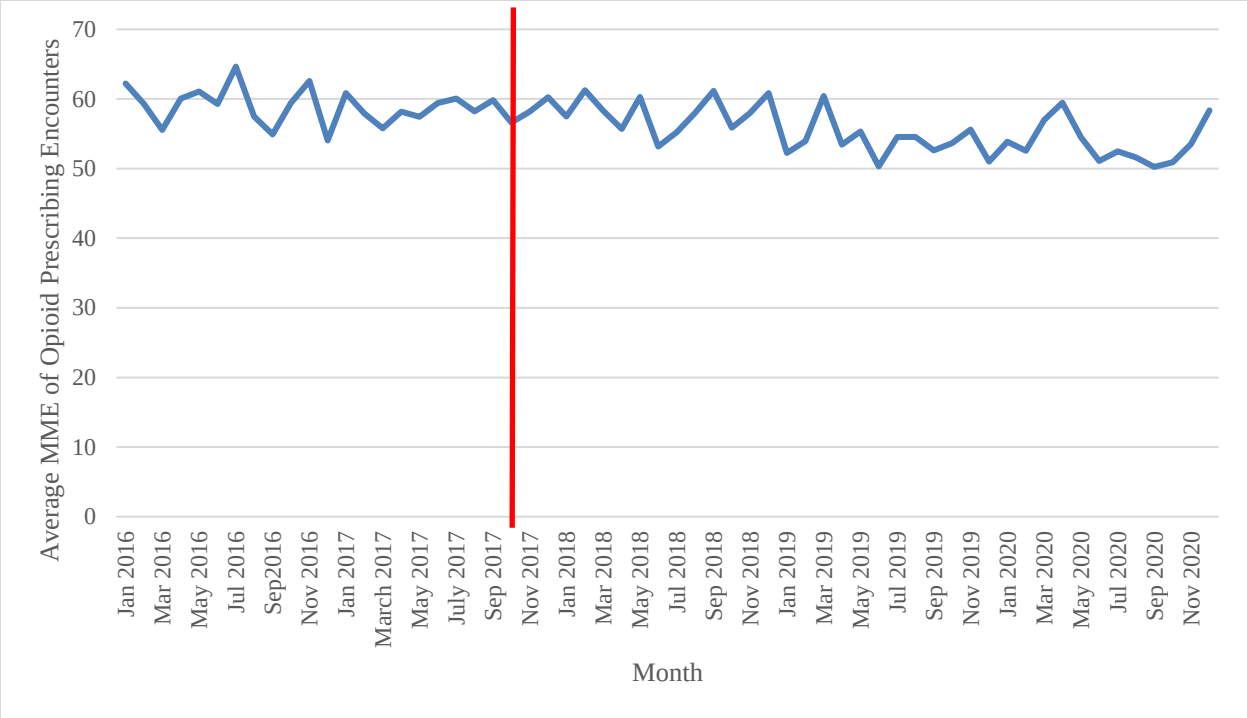

FIGURE 4C. AVERAGE MME OF OPIOID PRESCRIBING ENCOUNTERS OVER TIME
Note: The vertical line indicates when the clinical decision support intervention was implemented.

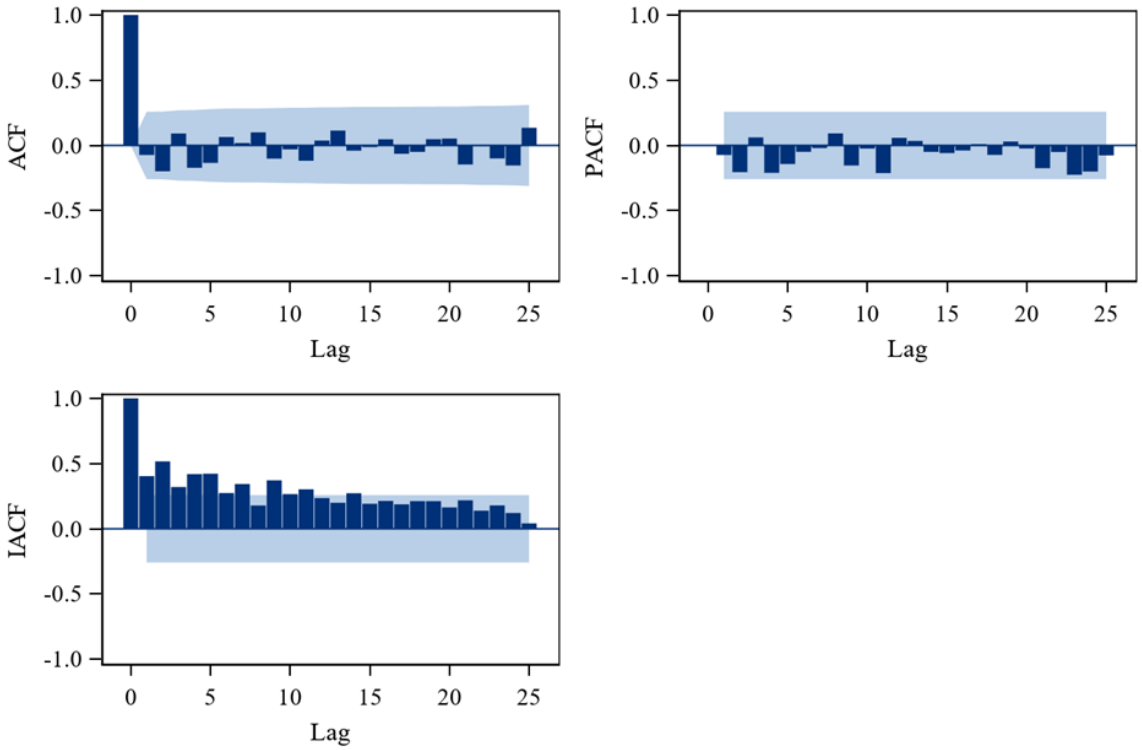

FIGURE 4D. AUTOCORRELATION FUNCTIONS OF THE TIME SERIES MODELING AVERAGE MME

TABLE 4C. INTERPRETATION OF REGRESSION COEFFICIENTS, INTERRUPTED TIME SERIES, AVERAGE MME

Parameter	Estimate	Standard Error	p-value	Interpretation
β_0	59.779	1.069	<0.0001	Intercept
β_1	-0.074	0.071	0.298	Trend Pre-Intervention
β_2	0.479	1.046	0.649	Change in Level Post-Intervention
β_3	-0.087	0.080	0.279	Change in Trend Post-Intervention
$\beta_1 + \beta_3$	-0.161	--	<0.0001	Trend Post-Intervention

Table 4D displays the results of the bivariate analyses assessing the association between prescriber and facility characteristics and the safe opioid prescribing score. Overall, the mean safe opioid prescribing score was 74.4%, and the median was 77.1%. The prescriber population was mostly physicians (73.1%), and the majority were family practice or internal medicine clinicians (86.1%). These prescribers prescribed opioids mostly to patients ages 18-64 (median 59.3% of patients), white patients (median 83.3% of patients), and female patients (median 60.6% of patients).The most common diagnosis among encounters with an opioid prescription was “other dorsopathies”. This diagnosis represented a median of 74.1% of opioid encounters for this group of prescribers. In contrast, the other diagnoses made up a small proportion of opioid prescribing encounters. The median number of patients prescribers gave an opioid prescription to for the included diagnoses during the study period was 42. About half of these prescribers practice at a large, multisite practice (52.5%), and very few (10.6%) practice at a clinic specializing in musculoskeletal conditions.

TABLE 4D. BIVARIATE ANALYSES COMPARING PRESCRIBER AND FACILITY CHARACTERISTICS AND SAFE OPIOID PRESCRIBING SCORE

	Sample n (%) Median (Q1,Q3) (n=606)	**Safe Opioid Prescribing Score Median (Q1,Q3); Spearman correlation coefficient**	**p-value**
Prescriber Characteristics			
Prescriber Type			
Physician	443 (73.1%)	80.8 (73.3, 87.5)	**<0.0001**
Advanced Practice Provider	163 (26.9%)	75.7 (64.2, 83.3)	
Specialty			
Family Practice/Internal Medicine	522 (86.1%)	76.4 (66.0, 84.6)	**0.1240**
MSK	65 (10.7%)	78.6 (73.5, 85.5)	
Other	19 (3.1%)	77.8 (71.9, 92.3)	
Case Mix – Age			
Percent Patients <18	0 (0, 0)	-0.035	0.3929
Percent Patients 18-64	59.3 (48.4, 70.5)	0.245	**<0.0001**
Percent Patients ≥65	40.7 (29.5, 51.6)	-0.244	**<0.0001**
Case Mix – Race			
Percent Patients White	83.3 (71.8, 91.4)	-0.269	**<0.0001**
Percent Patients Black	14.8 (7.1, 24.1)	0.255	**<0.0001**
Percent Patients Other	0 (0, 2.3)	0.021	0.6099
Case Mix – Gender			
Percent Patients Female	60.6 (51.8, 71.0)	0.115	**0.0045**
Case Mix – Diagnosis			
Percent Encounters Dorsopathy	0 (0, 1.5)	-0.133	**0.0011**
Percent Encounters Inflammatory Polyarthropathy	6.8 (3.6, 11.1)	-0.058	**0.1539**
Percent Encounters Osteoarthritis	18.5 (9.4, 30.7)	-0.045	0.2650
Percent Encounters Other Dorsopathy	74.1 (58.8, 83.3)	0.037	0.3580
Percent Encounters Spondylopathy	5.7 (2.0, 11.1)	-0.113	**0.0054**
Number of Patients	42.0 (20.0, 88.0)	-0.408	**<0.0001**
Facility Characteristics			
Large, Multisite Practice			
Yes	318 (52.5%)	78.6 (69.3, 86.7)	**<0.0001**
No	288 (47.5%)	75.0 (63.9, 82.6)	
MSK Specialty Clinic			
Yes	64 (10.6%)	78.6 (73.6, 85.5)	**0.1201**
No	542 (89.4%)	76.9 (66.1, 84.6)	

I included the variables that were significant at the $p<0.2$ level in a multivariable linear regression model presented in Table 4E. Furthermore, I excluded number of encounters because it was highly correlated with number of patients. I chose number of patients because the R^2 value was higher including number of patients as compared to including number of encounters. Similarly, because the age and race variables were highly correlated with each other, I only included the percent of patients age 18-64 and the percent of patients who were white in the model. Using these same variables, the model building process proceeded as shown in Table 4F. Inclusion of random slopes for each of the prescriber-level covariates produced too complex of a model; therefore, I fit models including each prescriber-level covariate as a random slope individually. The only prescriber-level covariates which were statistically significant as a random slope were the percent of patients who were white and the number of patients. By including both of these in the model, the percent of patients who were white was no longer statistically significant, and the model fit did not improve by including it. Therefore, Model 3 only includes the number of patients as a random slope. While the BIC was slightly higher for Model 4 as compared to Model 3, the difference was not substantial. Thus, I selected Model 4 to align with the conceptual model of important covariates at both the prescriber and facility levels.

TABLE 4E. MULTIVARIABLE LINEAR REGRESSION, SAFE OPIOID PRESCRIBING SCORE

	Estimate	**p-value**
Intercept	86.1	<0.001
Prescriber Characteristics		
Prescriber Type		
Physician	--	--
Advanced Practice Provider	4.70	0.0002
Specialty		
Family Practice/Internal Medicine	--	--
MSK	2.59	0.5355
Other	0.13	0.9649
Case Mix – Age		
Percent Patients 18-64	0.09	0.0060
Case Mix – Race		
Percent Patients White	-0.16	<0.0001
Case Mix – Gender		
Percent Patients Female	0.05	0.2482
Case Mix – Diagnosis		
Percent Encounters Dorsopathy	-0.22	0.3035
Percent Encounters Inflammatory Polyarthropathy	-0.04	0.3654
Percent Encounters Spondylopathy	0.05	0.4660
Number of Patients	-0.08	<0.0001
Facility Characteristics		
Large, Multisite Practice		
Yes	2.77	0.0113
No	--	--
MSK Specialty Clinic		
Yes	1.87	0.6465
No	--	--

TABLE 4F. ESTIMATES FOR TWO-LEVEL LINEAR MIXED EFFECTS MODELS OF SAFE OPIOID PRESCRIBING SCORE (N=606)

	Model 1	**Model 2**	**Model 3**	**Model 4[a]**
Model Description	**No predictors, just random effects for intercept**	**Model 1 + Prescriber level fixed effects**	**Model 2 + random slopes for prescriber level predictors**	**Model 3 + Facility level fixed effects**
Fixed Effects				
Intercept Estimate (standard error)	**73.26 (1.12)**	**83.52 (4.84)**	**84.57 (4.71)**	**83.97 (4.72)**
Prescriber Type				
Physician		--	--	--
Advanced Practice Provider		**2.96 (1.21)**	**2.82 (1.18)**	**2.92 (1.19)**
Specialty				
Family Practice/Internal Medicine		--	--	--
MSK		2.08 (2.93)	0.77 (2.81)	2.39 (3.80)
Other		-1.70 (2.97)	-1.64 (2.89)	-1.20 (2.90)
Case Mix – Age				
Percent Patients 18-64		**0.08 (0.03)**	**0.08 (0.03)**	**0.08 (0.03)**
Case Mix – Race				
Percent Patients White		**-0.17 (0.03)**	**-0.16 (0.03)**	**-0.17 (0.03)**
Case Mix – Gender				
Percent Patients Female		0.05 (0.04)	0.05 (0.04)	0.04 (0.04)
Case Mix – Diagnosis				
Percent Encounters Dorsopathy		-0.13 (0.20)	-0.15 (0.19)	-0.13 (0.19)
Percent Encounters Inflammatory Polyarthropathy		0.01 (0.06)	0.03 (0.05)	0.03 (0.05)
Percent Encounters Spondylopathy		0.08 (0.06)	0.05 (0.06)	0.06 (0.06)
Number of Patients		**-0.10 (0.01)**	**-0.11 (0.01)**	**-0.11 (0.01)**
Large, Multisite Practice				
Yes				**3.75 (1.87)**
No				--
MSK Specialty Clinic				
Yes				-4.65 (4.51)
No				
Error Variance				
Level-2 (Attending) Intercept	**54.60 (16.34)**	**39.58 (11.36)**	**27.87 (10.53)**	**25.62 (9.74)**
Random Effects				
Number of Patients$_{Site}$			**0.002 (0.001)**	**0.002 (0.001)**
Model Fit				
AIC	4938.5	4759.4	4747.8	4747.1
BIC	4945.6	4790.2	4781.0	4785.0

Note: Bold indicates $p<0.05$; $ICC_{Site} = 0.2354$; Values based on SAS PROC MIXED. Estimation Model = Maximum Likelihood. Parameter estimates are shown with standard errors in parentheses.
[a] Best fitting model

Based on the intraclass correlation coefficient (ICC) calculation, 23.5% of the variance in safe opioid prescribing score is accounted for by site. Thus, approximately 76.5% remains to be accounted for by prescriber factors. Advanced practice providers were associated with an increase in opioid prescribing score of 2.92 percentage points. As percentage of patients age 18-

64 increases, safe opioid prescribing score also increases. On the other hand, as the percent of white patients increases, and as the number of patients prescribed opioids increases, safe opioid prescribing score decreases. At the facility level, large, multisite practices were associated with an increase in safe opioid prescribing score of 3.75 percentage points.

Discussion

Overall, the implementation of a clinical decision support platform to operationalize the CDC Guideline for Prescribing Opioids for Chronic Pain had a statistically significant influence on the percentage of encounters resulting in an opioid prescription. However, the influence was small. The percent of encounters resulting in an opioid prescription after the intervention was implemented was 1.6% lower than it was prior to the intervention ($p=0.0002$). The significant trends before and after the intervention indicate a gradual reduction over time. This reduction is most likely due to other factors, such as increased awareness of the harmful effects of opioids, increased oversight of opioid prescriptions by the healthcare system, changes in legislation, and/or changes in patient preferences. The small effect of this intervention is not surprising, as the intervention was aimed toward prescribing opioids safely rather than preventing opioid prescriptions. However, the trend is encouraging, showing that while almost 18% of patients received an opioid at the beginning of the study period, only approximately 8% received opioids at the end of the study period. In comparison, patients with osteoarthritis reportedly receive opioids 27% of the time – a rate higher than any time point in the present study.[52] These results align with recommendations that opioids are typically not necessary for these chronic musculoskeletal conditions.

The average MME was approximately 50-60 throughout the study period, which is a dose which aligns with the CDC Guideline recommendation of less than 90 MME. The intervention

was not associated with a change in the average MME of prescriptions. The slope of average MME did decline significantly after the intervention ($p<0.0001$), with MME declining by 0.16 MME per month. This difference is unlikely to be clinically significant but could be due to a reduction in very high dose opioid prescriptions. An interrupted time series analysis of nationwide data did find a downward trend in high dose prescriptions as well as overall opioid prescribing rate prior to the release of the CDC guideline, but an even greater decrease following the guideline release.[16] To determine the impact on high dose prescriptions, future studies may assess the percent of opioids >90 MME over time in this specific population rather than average MME. As there was no statistically significant level change post-intervention, I cannot attribute this trend to the clinical decision support intervention.

Previous studies conducted in the emergency department have found significant effects of clinical decision support interventions on whether patients received opioids and MME. However, one of the studies did not account for ongoing trends during the study period, other than conducting the intervention at two separate hospitals at different times (a few months apart).[26] This study design could miss the impact of long-term trends. The other study was a randomized controlled trial, which would control for trends outside the intervention. However, it was conducted with very few patients (n=40) who were diagnosed with opioid use disorder. An intervention in Louisiana found no reduction in MME after implementation of a clinical decision support intervention, but did find an increase in use of urine drug screens and naloxone prescriptions.[64] In summary, each clinical decision support intervention is unique in its design, making it challenging to synthesize the literature. Therefore, research which aims at rigorously testing a specific intervention and disseminating interventions deemed efficacious should be an

area of focus for researchers, healthcare administrators, electronic medical record vendors, and government agencies funding research in this space.

Using the safe opioid prescribing composite score, the median score for prescribers treating at least 10 patients in the post-intervention period was 77.1%. A considerable amount of variation in this score was accounted for by practice site (23.5%). Another study using a mixed effects model accounting for clustering of patients within practices found a significant amount of variation in multiple opioid prescribing practices explained by practice.[65] The hierarchical model identified two prescriber-level factors associated with a higher safe opioid prescribing score: the percent of patients ages 18-64 and the prescriber being an advanced practice provider. Two studies in the literature indicate that advanced practice providers prescribe higher MMEs and have more outliers prescribing high-frequency or high-dose opioids as compared to physicians.[66,67] However, neither of these studies was conducted in the context of a clinical decision support intervention. Advanced practice providers may change their behavior in response to clinical decision support tools. On the other hand, two prescriber-level factors were associated with a lower safe opioid prescribing score: the percent of patients who are white and the total number of patients to whom that clinician prescribed an opioid. The literature consistently demonstrates that white patients are more likely to receive opioids as compared with black patients.[68-73] Additionally, one study did find that black patients were more likely to receive guideline-concordant care (i.e., urine drug testing, regular office visits, restricted early refills) as compared to white patients[74], which aligns with the findings in this study. Clinicians who prescribe to more patients may have a patient population that is more likely to require opioids or they may be treating patients who were referred to them and already established on opioids. On the other hand, since opioids are not generally recommended for this patient

population, clinicians who are prescribing to a lot of patients may be less aware of current practice guidelines and evidence. Future research could explore these hypotheses. The effect of the number of patients may also be due to the formula for calculating the safe opioid prescribing score. Clinicians who prescribe to more patients have more opportunities to not adhere to guidelines, producing a lower score. Prescribers with fewer patients must follow guidelines almost perfectly to have a high score. Additionally, the more prescriptions one writes, the higher the odds of receiving one of the alerts that contributes to the score. A prescriber with few patients may not receive any alerts; therefore, his or her score would depend solely upon MME. Since the median MME in this population falls below 90, it is expected that prescribers who do not encounter any alerts would have a high score. Further research is needed to validate the safe opioid prescribing measure and understand the relative importance of each of the behaviors included in the composite score. Interestingly, while the number of patients was a significant prescriber-level covariate, the random slope of number of patients by site was also statistically significant. This finding means that the influence of number of patients on the safe opioid prescribing score differed significantly by practice site. Sites may have internal policies and practices which cause these differences. For example, some practices may designate a few clinicians to treat patients requiring opioids, while others distribute these patients among their clinicians.

Only one site-level covariate was statistically significant. Practices that were large, defined as having multiple physical locations, were associated with higher safe opioid prescribing scores. It might be that these large practices are more likely to have formal policies and procedures to reduce variation in practice among their clinicians. Additionally, these

practices may have more resources to engage in activities such as quality improvement initiatives.

One limitation of this analysis is using diagnosis codes to identify patient encounters. These are chronic conditions that are likely to be included on any encounter the patient has with his or her primary care clinician. However, I am unable to know for certain whether the opioid was prescribed for the musculoskeletal condition. It is possible the patient also had an acute injury or other condition requiring opioids. I did remove encounters associated with cancer; however, it is impossible to rule out all other indications for an opioid. Another limitation is the fact that the case mix variables are based only upon the patients receiving an opioid from that prescriber. The case mix of that clinicians entire patient panel would also be useful (i.e. do these conditions make up 80% of that clinician's panel or 20%). I was only able to obtain data for all patients (regardless of opioid prescription or diagnosis) by attending clinician. However, the person prescribing the opioid is not always the same as the attending. For example, advanced practice providers or trainees (residents and fellows) are rarely listed as attending, yet they prescribe a significant proportion of opioids in this healthcare system. Because my outcome was directly related to clinician response to alerts which appear upon opioid prescription, I decided it was more important to describe the actual prescriber's behavior, rather than attribute these behaviors to the attending on record. Finally, while the model identified a significant influence by site, as well as several important prescriber and facility variables, the model could likely be improved by the addition of variables which were not available for this analysis (i.e. clinician demographics, years of experience of the prescriber, and whether the practice is associated with an academic medical center). Finally, we were unable to test the impact of the intervention on

safe opioid prescribing behaviors because implementation of the clinical decision support platform itself allowed the measurement of these behaviors.

The interrupted time series design, correcting for autocorrelation, is a rigorous methodology for studying large scale interventions. The trend for both of these outcomes over time was declining, indicating a shift in clinical practice likely associated with many simultaneous factors. Without controlling for the trend over time, I could have mistakenly attributed the change from the pre-intervention to post-intervention period to the clinical decision support intervention. Similarly, the multilevel model is a more robust design to account for the nested structure of the data. The fact that many of the statistically significant associations in the bivariate and multivariable regression models were attenuated or no longer statistically significant in the multilevel model highlights the need for hierarchical modeling, particularly in the field of healthcare. This study used a relatively large sample of clinicians to assess the impact of a clinical decision support intervention on prescriber behavior. These results are likely generalizable to a broad range of primary care clinicians. Finally, I conceptualized and calculated an objective measure of safe opioid prescribing, based upon the CDC CPG. An objective measure such as this one would be useful both for research and for clinical practice to monitor clinician performance and identify opportunities for improvement and intervention.

These results demonstrate that clinicians are not prescribing opioids for chronic musculoskeletal conditions frequently, and that, when they do prescribe opioids, they are generally adhering to guidelines. Therefore, future research might explore the trend in outlier behavior over time (e.g., prescriptions over 90 MME). Additional data could be used to enhance the model to obtain a better fit, and interaction terms could be explored to understand how different covariates interact to influence safe opioid prescribing. These data can be used to

identify prescribers with very high and very low safe opioid prescribing scores for purposive sampling in a subsequent qualitative study to identify targets for intervention. For example, a qualitative case study could be designed to include practices with large variety in opioid prescribing scores to understand prescriber factors. Alternatively, a large, multisite practice with consistently high safe prescribing scores could be compared with a small practice with consistently low safe prescribing scores to identify practice characteristics that facilitate safe opioid prescribing.

The next steps could also include replicating this study with a broader range of chronic pain conditions outside of the musculoskeletal system to determine whether the same trends and patterns are present. While this study is significant because it included an objective measure of safe opioid prescribing, the composite score needs further validation. Future studies should assess the relative importance of each component of the score, as well as whether other behaviors should be added. Predictive validity could also be assessed by measuring the association between a prescriber's safe opioid prescribing score and outcomes such as opioid use disorder and opioid overdose. Validation of the score should include a broad range of clinicians and patients rather than the limited sample included in this study. For example, over half of the clinicians prescribed opioids to fewer than 10 patients in the approximately three-year period following the intervention and were thus excluded from the model.

Overall, the results of this study demonstrate clinicians are adhering to guidelines regarding opioid prescribing for patients with chronic musculoskeletal conditions. The implementation of a clinical decision support tool presented the opportunity to objectively measure safe opioid prescribing behavior. This measure could be used to assess the impact of future interventions in this healthcare system. Healthcare systems could also use this measure to

tailor interventions for certain prescribers or practices where safe opioid prescribing rates are low.

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Appendix 4A: Centers for Disease Control and Prevention Guideline Summary and Map to PRIMUM Intervention Component

Recommendation Statement	PRIMUM Intervention Component
1. Non-pharmacologic therapy and non-opioid pharmacologic therapy preferred.	Education
2. Establish treatment goals and set expectations.	**Standard pain agreement and prompt to complete at 90 days of opioid therapy**
3. Discuss risks and benefits of opioids.	Standard patient education printed with each prescription
4. Start with immediate-release opioids.	**Alert when ER/LA opioid selected for opioid naïve patient prompting immediate release instead.**
5. Prescribe lowest effective dose. Use caution above 50 and/or 90 MME/day	**Controlled Substance Review Component displays total MME. Alert if prescribing >50 or >90.**
6. Lowest effective dose, 3-7 days for acute pain.	Education, acute prescribing policy in progress
7. Evaluate within 1-4 weeks after starting and every 3 months after.	Reminder alert of guideline when patient reaches 90 days of opioids
8. Consider offering naloxone when factors increase risk.	**Alert to prescribe naloxone if history of overdose, above 50 MME, or current benzodiazepine**
9. Clinicians should review PDMP.	Hyperlink to PDMP on Controlled Substance Review Component
10. Clinicians should use urine drug screens	Alert suggesting urine drug testing at 90 days of opioid therapy.
11. Clinicians should avoid prescribing opioids and benzodiazepines concurrently.	**Alert to indicate co-prescription of opioids and benzodiazepines.**
12. Clinicians should offer or arrange evidence-based treatment for patients with opioid use disorder.	Education

Bold text indicates intervention components and behaviors assessed in the proposed study.

Appendix 4B: Musculoskeletal Conditions Included in Study

Diagnosis Code	Description	Parent Category	Diagnosis Category
M04	Autoinflammatory syndromes	Inflammatory polyarthropathies	Bone/joint
M05	Rheumatoid arthritis with rheumatoid factor	Inflammatory polyarthropathies	Bone/joint
M06	Other rheumatoid arthritis	Inflammatory polyarthropathies	Bone/joint
M07	Enteropathic arthropathies	Inflammatory polyarthropathies	Bone/joint
M08	Juvenile arthritis	Inflammatory polyarthropathies	Bone/joint
M10	Gout	Inflammatory polyarthropathies	Bone/joint
M11	Other crystal arthropathies	Inflammatory polyarthropathies	Bone/joint
M12	Other and unspecified arthropathy	Inflammatory polyarthropathies	Bone/joint
M13	Other arthritis	Inflammatory polyarthropathies	Bone/joint
M14	Arthropathies in other diseases classified elsewhere	Inflammatory polyarthropathies	Bone/joint
M15	Polyosteoarthritis	Osteoarthritis	Bone/joint
M16	Osteoarthritis of the hip	Osteoarthritis	Bone/joint
M17	Osteoarthritis of the knee	Osteoarthritis	Bone/joint
M18	Osteoarthritis of the first carpometacarpal joint	Osteoarthritis	Bone/joint
M19	Other and unspecified osteoarthritis	Osteoarthritis	Bone/joint
M40	Kyphosis and lordosis	Deforming dorsopathies	Spine
M41	Scoliosis	Deforming dorsopathies	Spine
M42	Spinal osteochondrosis	Deforming dorsopathies	Spine
M43	Other deforming dorsopathies	Deforming dorsopathies	Spine
M45	Ankylosing spondylitis	Spondylopathies	Spine
M46	Other inflammatory spondylopathies	Spondylopathies	Spine
M47	Spondylosis	Spondylopathies	Spine
M48	Other spondylopathies	Spondylopathies	Spine
M49	Spondylopathies in diseases classified elsewhere	Spondylopathies	Spine
M50	Cervical disc disorder	Other dorsopathies	Spine
M51	Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders	Other dorsopathies	Spine
M53	Other and unspecified dorsopathies, not elsewhere classified	Other dorsopathies	Spine
M54	Dorsalgia	Other dorsopathies	Spine

CHAPTER 5: DISCUSSION

Opioid overdose deaths have risen substantially over the past fifteen years, contributing to a reduction in life expectancy among Americans.[3] In contrast to illicit drug use, physicians and other prescribers played a role in contributing to the rise in opioid use and addiction through an increase in opioid prescribing. Physicians are also in a position to reverse this trend by following guidelines on appropriate and safe opioid prescribing. However, the position and beliefs of the medical community regarding opioids over time has not been described. Despite the proliferation of guidelines, interventions, and policies aimed at the medical community, the extent to which these actions have impacted clinical decision making and prescribing behavior has not been rigorously studied, accounting for simultaneous interventions and the nested structure of healthcare delivery systems, where individual clinicians are nested within practices.

My dissertation research addressed this gap by characterizing the experience of the medical community and measuring the multi-level factors influencing opioid prescribing within the context of legislation and clinical decision support interventions. I began by qualitatively describing the discourse around opioids among the medical community during the peak of the opioid epidemic to contextualize the legislation and clinical decision support interventions which I evaluated quantitatively. Collectively, this research and resulting manuscripts present a sophisticated and nuanced understanding of the multi-level factors which influence guideline-concordant opioid prescribing.

To describe the discourse around opioids among the medical community and identify which theoretical domains might be relevant to opioid prescribing behavior, I conducted a qualitative analysis of letters to the editor published in the *Journal of the American Medical Association*. This study aimed to identify which positions regarding the opioid epidemic are

prevalent among the medical community, the extent to which there is a professional consensus, and how the discourse has changed over time.

The majority of letters (n=39) were written in a neutral, objective manner, or they advocated for a balanced approach between appropriately treating pain while optimizing patient and community safety. Therefore, physicians overall did not display polarized views either against or for opioids. When authors wrote letters that were "opioid averse", they often wrote responses that were "balanced" or neutral after reading the response to their original letters. The medical community also had a consensus that the Joint Commission and FDA contributed to an environment that incentivized overprescribing and led to a rise in overdose deaths. Disagreement between authors was mostly around the interpretation of the medical literature.

In addition, the authors consistently discussed the themes of "blame" and "responsibility". Most often, physicians attributed blame to themselves; when discussing responsibility for actions to address the crisis, they called upon clinicians as well as other groups, most often the government and community. In the early time frame, there was one "opioid defense" letter, and the number of "opioid averse" letters increased after 2016. Over time, recommendations also moved from physician-focused recommendations to policy recommendations. The TDF domain most frequently included was environmental context and resources, which is consistent with calling on other groups to take action and turning toward policy and structures rather than individual clinician behavior.

This qualitative analysis framed and grounded my subsequent qualitative studies. The importance of environmental context and resources underscored the importance of accounting for multi-level factors in my subsequent analyses. I chose to assess the impact of both legislation and a clinical decision support intervention on opioid prescribing, which represent two examples

of recommendations discussed in these letters. Both studies utilized a time series analysis to rigorously measure the impact of the intervention or policy, and both used a hierarchical multivariate regression model to appropriately account for the nested delivery of healthcare (i.e., prescribers within practices). While both studies assessed outcomes of opioid prescribing, one focused on the duration of opioids given for acute musculoskeletal pain, while the other focused on guideline-concordant opioid prescribing for patients with chronic musculoskeletal pain. Both of these outcomes fit within the concept of "balance", as the goal for either situation is not to avoid opioids altogether but rather to adhere to guidelines which address pain while minimizing adverse outcomes associated with opioid use.

I chose to assess the influence of the STOP Act legislation on the percentage of opioid prescriptions written for seven days or less associated and the patient, physician, and facility factors which predicted adherence to the mandated duration limits. I restricted to patients presenting with acute musculoskeletal injury in a large healthcare system in North Carolina from 2016-2020 (n=12,918 patients total; n=6,849 patients after STOP Act). I found there was a 17.7% increase in prescriptions written for 7 days or less after the STOP Act as compared to before ($p<0.001$), even after adjusting for the significant trend before the implementation of STOP Act. After STOP Act was implemented, opioids were prescribed for less than 7 days in 77.1% of encounters, with 30% of variation accounted for by physician and another 9% by facility. Patients receiving more than one opioid and those that had received opioids at the hospital or ED twice in the previous month had reduced odds of receiving a prescription less than 7 days, as well as patients with shoulder injuries. The influence of shoulder injury also differed significantly by physician. At the physician level, sports medicine clinicians were less likely to

adhere to duration limits as compared to orthopaedic surgeons. Altogether, these results show significant potential for legislation to effect physician behavior change.

In my final paper, I chose to measure the influence of a clinical decision support intervention launched throughout a large healthcare system on opioid prescribing outcomes with the goal of operationalizing and implementing the 2016 CDC Guideline for prescribing opioids for chronic pain (n=1,290,7467 encounters total; n=154,299 encounters with an opioid prescription; n=81,867 encounters with an opioid prescription initiated during the post-intervention time period). I restricted to patients presenting with chronic musculoskeletal conditions (arthropathies and chronic conditions of the spine) because they are common chronic pain conditions for which opioids are not shown to be very effective. The time series analysis measured the effect of the clinical decision support intervention on two outcomes – the percent of patients receiving an opioid prescription, and the average dose of opioid prescriptions among those receiving a prescription. Overall, this intervention had a statistically significant but small impact on outcomes. The percentage of encounters resulting in an opioid prescription after the intervention was 1.6% lower than before the intervention (p=0.0002). There were also statistically significant trends both before and after the intervention, indicating a gradual reduction over time, most likely due to other factors (e.g., changes in legislation, increased awareness, patient preferences). Despite the gradual nature, the trend was substantial, with almost 18% of patients receiving opioids at the beginning of the study compared to only 8% at the end. There was not a change in average opioid dose associated with the intervention. There was a statistically significant yet clinically insignificant reduction in MME after the intervention (-0.16 MME per month). Overall, the MME was between 50 and 60 throughout the study period, which aligns with guidelines.

I conceptualized a composite safe opioid prescribing score as the outcome for the hierarchical regression model. The composite score was a weighted average of the following behaviors: 1) cancelling a prescription when alerted that he/she is going to prescribe an opioid when the patient is already prescribed a benzodiazepine; 2) initiating a pain agreement when prompted that a patient has reached over 90 days of continuous opioid therapy; 3) prescribing naloxone when alerted that the patient is at high risk for overdose; 4) canceling a prescription for an extended release opioid when alerted that patient is opioid naïve; and 5) prescribing opioids less than 90 MME. Overall, the median safe opioid prescribing score in the post-intervention period was 77.1%, with 24% of the variation accounted for by practice site. The launch of the intervention allowed detailed data capture of physician behavior in response to the clinical decision support tools that unfortunately was not feasible prior to the intervention. The percent of patients between ages 18-64 that a prescriber treated was associated with a safer opioid prescribing pattern. Advanced practice providers also had higher safe opioid prescribing scores as compared to physicians. On the other hand, the percent of patients the prescriber treated who were white and the number of patients a clinician prescribed an opioid to were associated with lower scores. At the practice level, those which were large and had multiple physical locations had higher safe opioid prescribing scores.

Collective Implications

These findings have significant implications for both public health research and practice both individually and collectively. The qualitative analysis of letters to the editor underscored the importance of the environmental context and resources in relation to opioid prescribing. In addition, those findings emphasized that, while individual prescriber behavior is important,

simultaneously engaging partners outside the clinical setting and focusing on changing policies and structures are critical.

The analysis of the STOP Act legislation found that legislation was associated with significant and immediate changes in physician behavior, even six months prior to the law going into effect. Therefore, it may not be necessary to dedicate significant resources into surveillance of physician behavior or enforcement of legislation. The multilevel model did find differences in adherence to legislation by specialty, which highlights the need for targeted interventions. For example, hospitals could use this information to design and tailor additional interventions for populations where adherence to duration limits were lower (e.g., shoulder injury, sport medicine). Delegating resources this way would not only be more cost effective by focusing on subpopulations but would likely have a greater effect since interventions could be tailored to specific situations.

The analysis of the impact of a clinical decision support intervention to operationalize the CDC Guideline found only a small effect on opioid prescribing and dosage. Because the intervention was designed to promote safe opioid prescribing and not to reduce opioid prescribing, this finding is not surprising and serves as a reminder for public health researchers and health services researchers to design research studies and program evaluation with outcomes measures consistent with the behavior the intervention targets. In this case, the development of the intervention created the ability to measure physician behavior; thus, these outcomes were chosen as proxies. My study also found that larger practices were associated with safer opioid prescribing. Larger practices may have formal policies and more resources, which is consistent with the environmental context and resources theme identified in the first paper. Healthcare systems may use this information to connect smaller practices with larger ones in an effort to

support the smaller practices in the implementation of evidence-based practices. Finally, the development of a quantitative and objective safe opioid prescribing composite score can inform both research and quality improvement initiatives.

Collectively, these studies highlight the importance of focusing on the environment in which clinicians function and not only the individual clinician. Within the healthcare setting, these analyses found 9% of variation in opioid prescription duration and 24% of variation in safe opioid prescribing to be due to practice site. Furthermore, many of the statistically significant associations in the bivariate and multivariable regression models were attenuated or no longer significant in the multilevel models, demonstrating the necessity for more advanced modeling to account for the nested organization of healthcare delivery.

Outside of healthcare, these findings demonstrate that rigorous research is needed to explore the effect of interventions across sectors that are happening simultaneously to efficiently guide decision making and policy. Specifically, local governments will soon receive funds from opioid manufacturers due to litigation against pharmaceutical companies for their role in the epidemic.[56] High-quality scientific evidence must be leveraged to guide the distribution of these resources. Furthermore, researchers and healthcare administrators must look beyond the clinical setting and partner with government, industry, insurance companies, and regulatory agencies to create systemic change.[57] This approach is consistent with the social ecological model and the Health in All Policies approach.[58,59]

Finally, both quantitative analyses demonstrate the fact that healthcare delivery is team-based rather than an individual clinician's behavior. Both studies wrestled with the fact that the attending physician is not always the person who prescribes medications. Future studies should conceptualize prescribing behavior at the team level rather than individual level. While

understanding and intervening on prescribing behavior is important, researchers should not lose focus on assessing downstream patient outcomes, including both opioid use disorder and overdose and pain management. While physicians advocated for a balance between both of these constructs, research is needed to determine whether changes in opioid prescribing behaviors are having the expected outcome for population health.

Overall Limitations

The limitations of each specific study are addressed in the individual chapters, but cross-cutting limitations include the reliance on diagnosis codes to identify populations, the inability to know the reason for the opioid prescription, the decision to focus on *either* the attending or the prescriber, the lack of data which might improve model fit. The orthopaedic literature has demonstrated several times that coding is inaccurate.[60-63] However, it is the most practical and feasible method to identify patients using large, electronic medical record databases. Prescribers are also not required in all electronic health records to specify the diagnosis associated with a prescription medication. While such a requirement would potentially improve the validity of research findings, it is unknown whether those data would be inaccurate (similar to diagnosis codes) and whether it would impede productivity and/or satisfaction among clinicians. The STOP Act analysis made the assumption that attending physicians are responsible for the care of their patients, including prescriptions written by other clinicians. On the other hand, the analysis of safe opioid prescribing behaviors attributed behaviors to individual prescribers, who may have been making decisions based on attending preference. These assumptions may not accurately reflect what is happening in clinical practice. Finally, the models could be improved by including variables which were not available in these datasets (e.g., physician demographics, insurer, interaction between physician and patient characteristics, and whether the clinician is employed

by the healthcare system or an external group. I was unable to test the impact of the clinical decision support intervention on safe opioid prescribing behaviors because the implementation of the clinical decision support platform itself created the capacity to measure the behaviors. Future research could address this limitation using rigorous and practical research designs such as stepped wedge randomization or multiple baseline designs.[64,65] Finally, these results are generalizable only to musculoskeletal patients and clinicians.

Study Strengths

The use of mixed methods to gain a rich understanding of factors influencing clinical decision making regarding opioid prescribing is the main strength of my research. The findings from the qualitative study provided context for understanding the implications and findings of the quantitative studies. Similarly, by studying two different types of interventions (legislation and clinical decision support) and two different patient populations (acute pain and chronic pain), my research yields new knowledge which can be applied across a broad range of research and practice. Furthermore, findings which were consistent across all three papers have increased validity due to triangulation. For example, the qualitative paper identified the environmental context as an important factor, and both quantitative analyses determined practice site accounted for considerable variation in individual prescriber behavior.

The interrupted time series and hierarchical multivariate regression models are a second significant strength of this research. As demonstrated in the content analysis, many different stakeholders are enacting policies or implementing interventions to address the opioid crisis simultaneously. Accounting for trends for multiple years before and after each intervention, while accounting for autocorrelation, yields a more precise estimate of the unique impact of a single intervention. The multilevel modeling is not only theoretically best suited for the way healthcare is organized and structured, but I found that results changed between the standard

logistic or linear regression and the model accounting for the nested structure. Studies which do not control for this organization may yield inaccurate findings.

Results of the quantitative analyses are likely generalizable to clinicians treating musculoskeletal pain across the country, since the data were derived from a large healthcare system spanning a few states over a five year period. Finally, I conceptualized and developed an objective composite measure of safe opioid prescribing, based on the CDC Guideline for prescribing opioids for chronic pain. This measure needs further validation but is a first step toward a method for researchers to measure guideline concordant pain management, including both opioid prescribing behavior (i.e., opioid dose) as well as patient safety measures (i.e., prescribing naloxone). A measure like this is necessary to depict a balanced view of a physician's clinical decision making and practice, between opioid stewardship and pain management.

Future Directions

These results lay the foundation for future studies to replicate analyses with different populations, use qualitative analyses to expand upon the quantitative findings, and validate the safe opioid prescribing measure. For example, the content analysis can be replicated with a variety of academic journals from across specialties to look for variation in themes, or the discourse in academic journals can be contrasted with letters printed in the lay press. The impact of the STOP Act should also be explored for other specialties treating musculoskeletal injuries, such as family medicine or emergency medicine, for other acute pain diagnoses (e.g., headaches), and for postsurgical pain. Adding a comparison state without such legislation or states with different legislation would also be worthwhile. The impact of the clinical decision support intervention can also be replicated for other chronic pain conditions, such as fibromyalgia or neuralgias. In addition to replication, expanding the models to include additional

variables or interaction terms might improve the model fit. Finally, assessing trends over time in outlier behavior (such as prescriptions over 90 MME) might highlight different patterns than measuring guideline concordant behavior, particularly in the case where physicians are very frequently following guidelines. Identifying predictors of outlier behavior would allow healthcare systems to target resources to the outliers rather than all physicians and practices.

Another direction for future research is to use the quantitative findings to pursue sequential mixed methods studies by using the quantitative data to create a purposive sampling strategy for a subsequent qualitative study. For example, I could identify prescribers who routinely adhere to duration limits and prescribers that rarely adhere to duration limits to contrast those groups and identify targets for intervention. Similarly, I could select practices with large variety in opioid prescribing scores to understand the relevant prescriber factors. To identify practice characteristics that facilitate safe opioid prescribing, I could compare a large, multisite practice with consistently high safe prescribing scores and a small practice with consistently low safe prescribing scores.

The content analysis demonstrated differences in use of the literature and formation of beliefs across physicians. Similarly, the STOP Act findings indicated differences in behavior by specialty. I would like to further explore the role of identity, social influences, and decision processes on the formation of beliefs, clinical decision making, and clinical practice.

Finally, I want to pursue formal psychometric validation of the safe opioid prescribing measure. The relative importance of each behavior included in the score is unknown. Additionally, the score needs to be explored among a much larger group of physicians. The predictive validity of the measure will be critical for the score to have utility in practice;

therefore, I would like to assess the correlation between prescribing scores and outcomes such as opioid use disorder and overdose.

Conclusion

Drug overdose deaths continue to have a significant impact on population health in the United States, with over 70,000 deaths in 2019.[66] This research furthered scientific knowledge regarding the physician experience of the opioid epidemic and associated legislation and interventions. Balancing providing adequate pain management and preventing adverse effects associated with opioids, including opioid use disorder and death is the medical community's goal. However, they need an environment which supports that goal and the resources to succeed. The insights gained from this research may inform multilevel policies and interventions which comprehensively and effectively address opioid safety.

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APPENDIX A: ETHICAL APPROVAL LETTERS

CHARLOTTE
RESEARCH AND ECONOMIC DEVELOPMENT

To:	Meghan Wally University of North Carolina at Charlotte
From:	Office of Research Protections and Integrity
Date:	03-Sep-2021
Expiration Date of Approval by External IRB:	31-Aug-2022
RE:	Agreement to Rely on External IRB
Study #:	IRB-M-21-0402
External Organization:	Atrium Health
Study Title:	Prescription Reporting with Immediate Medication Utilization Mapping (PRIMUM)

This confirms that an IRB Authorization Agreement with the organization identified above is in place and UNC Charlotte continues to rely on the external IRB for continuing oversight of this study. This agreement specifies the roles and responsibilities of the respective entities.

Study Description:
This study will utilize an existing dataset of opioid prescriptions at a large healthcare system to determine whether implementation of legislation and/or a clinical decision support intervention is associated with improved opioid prescribing. The study will also determine which patient, prescriber, and facility characteristics are associated with opioid prescribing behaviors. The results of this research can be integrated to inform future interventions to address opioid safety.

It is your responsibility to:

1. Inform the UNC Charlotte IRB about any actions by the external IRB affecting their approval to conduct the study, including suspension or termination of approval.
2. Submit a modification to the UNC Charlotte IRB (via Niner Research) if/when new personnel are added to the study team or the study is modified in such a way that additional institutional approvals are required (e.g., radiation safety, biosafety).
3. Submit a copy of the external IRB approval letter and current approved consent document to the UNC Charlotte IRB (via Niner Research) when the study is renewed; you will continue to receive reminder notices from the UNC Charlotte IRB for renewal, and should provide the external approval

and consent documents within 30 days of receipt.

4. **Report all Unanticipated Problems protocol violations and unresolved subject complaints to the** UNC Charlotte IRB *in addition to the external IRB*. You may submit a copy of the report you submitted to the external IRB; this should be done via the Adverse Event form in Niner Research.
5. Maintain compliance with all other UNC Charlotte policies (e.g., data security, conflict of interest).