Themes and gaps in research for opioid use and misuse pertinent to orthopaedic injury patients

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Abstract

Introduction: Prescription opioid use and misuse has accelerated rapidly in the United States over the past 2 decades. Orthopaedic surgeons are the third highest prescribers of opioids, and thus are contributing to this problem at a significant rate. Despite a surge in the number of publications on this issue, there has been little emphasis in the literature on disentangling the various factors contributing to opioid use and misuse among fracture patients. The goal of this study was to describe areas of focus and identify knowledge gaps present in the current literature on this important issue.

Methods: We employed a scoping review technique due to its ability to successfully address a broad research question. In order to better understand the type of information deemed relevant by opioid researchers, we further analyzed our search results by sorting the publications into the following categories: consumer-focused, provider-focused, focus on substitutes, industry-focused, and focus on regulations (at the institution, profession, and government level).

Results: The search strategies generated 8760 citations; of these, 1166 publications satisfied our inclusion criteria. Around 607 of these final abstracts were marked as “extremely relevant” (52%) and the other 559 (48%) were marked “relevant.” About 36.4% of the total included articles applied to the providers and 19.6% provided information on the consumer. A total of 25.2% of the included papers concerned substitutes for opioids, 15.7% focused on regulatory power in the opioid industry, and 14% considered opioids as an industry, including power of both current stakeholders and potential new entrants.

Discussion: The present study provides a thorough summary of existing literature on opioid use and misuse relevant to musculoskeletal trauma patients. Furthermore, the categorical division of the literature provides a unique perspective into the drivers contributing to the opioid epidemic, and may assist in development of effective interventions to reduce excessive opioid use following traumatic injuries. Our review allowed us to identify important aspects of the opioid industry and various drivers of abuse that were absent from the literature including involvement of the pharmaceutical industry on the opioid epidemic, the involvement of insurance companies in opioid distribution, and the use of nonopioid alternative medications such as nonsteroidal anti-inflammatory drugs (NSAIDs).

Keywords: literature review, musculoskeletal trauma, opioid epidemic, opioid misuse, opioids, orthopaedic injury

1. Background

Pain, considered by some as the “fifth vital sign,” accounts for 80% of physician visits in the United States.\textsuperscript{[1]} As the incidence of pain-related doctor visits has skyrocketed, nontherapeutic opioid use has, unsurprisingly, increased threefold in the United States since the late 1990s.\textsuperscript{[2]} Similarly, as the morbidity and mortality associated with prolonged opioid use has become better understood so has the scrutiny placed on the prescribing of these medications increased dramatically.\textsuperscript{[3]} The substantial risk for physical dependence, addiction, and overdose requires that medical professionals from all specialties re-evaluate their opioid prescribing practices.

Due to the severity of pain associated with fractures and traumatic musculoskeletal injuries, orthopaedic surgeons are the third-largest prescriber of opioids in the United States.\textsuperscript{[4]} Around 69% of long bone fracture patients reporting to emergency departments are prescribed opioids by their physicians.\textsuperscript{[5]} In fact, fracture patients are twice as likely to be prescribed opioids as nonfracture patients.\textsuperscript{[6]} Furthermore, a case-control study at the University of Utah found that orthopaedic trauma patients are significantly more likely than the general population to use prescription opioids prior to injury. This history of opioid use renders these patients 6 times more likely to exhibit long-term use after injury than the general population.\textsuperscript{[7]} Although intended as a measure for reducing acute pain, many orthopaedic opioid prescriptions are continued throughout the recovery phase when nonopioid analgesics may be more appropriate. This is despite the serious potential side effects, including constipation, respiratory depression, and pain hypersensitivity.\textsuperscript{[8]} In spite of the numerous associations between opioid prescriptions and

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orthopaedics, there is a surprising lack of literature reviewing the role of opioid use in the orthopaedic trauma population.

While an overwhelming amount of literature about chronic pain treatment has been summarized, chronic pain has not been studied through the lens of an orthopaedic trauma population. The purpose of this study was to address the question: “What opioid-related literature can be examined and applied to the field of orthopaedic trauma?” The long-term vision of this study is to provide a comprehensive summary of the available literature in order to improve the health of patients with orthopaedic injuries, inform parties with a stake in health policy about the issue, and reduce the consequences and risks of opioid use.

2. Methods and materials

2.1. Overview

Due to our broad research question, we recognized that a novel knowledge synthesis method would be necessary to achieve our study objective. A scoping review is an increasingly popular method used to review broad topics in order to better understand the range of a field. Unlike systematic reviews or meta-analyses, which are valuable data synthesis techniques for narrow research questions in areas of homogeneous data, scoping reviews aim to map or summarize a range of evidence or communicate the current depth of research in an area. Scoping reviews typically address large research questions by allowing inclusion of multiple interventions, study designs, and types of publications. This includes publications such as policy papers and editorials, which are invaluable resources when assessing a public health concern such as opioid abuse. Furthermore, while scoping review methodologies are more flexible than systematic reviews for including diverse data sources, both review techniques rely on transparent, reproducible, and comprehensive search strategies; the scoping review should not be confused with a narrative review in which the authors can choose their data sources without accountability. Thus, to explore opioid use in this population, we employed a scoping review method.

No human subjects were involved in the study and as a result there was no need for research ethics committee approval or informed consent.

2.2. Literature search

In consultation with a biomedical librarian, we generated several search strategies designed to be sensitive for diverse areas of opioid research. We used various keywords, MeSH (medical subject heading) terms, and the Emtree Thesaurus to search the following electronic databases: Medline, EMBASE, PsychInfo, and Guidelines.gov. All searches were performed in June 2016. Because this review is focused on the changes that have occurred over the past 2 decades to result in the dramatic increase in prescription opioid misuse and abuse, we only included papers published after 1996. While performing the search, we used a filter of “human only” research. The details of the search strategies are addressed in Table 1.

2.3. Study selection

Results from all database searches were organized into a literature management program (Refworks) where they were screened for duplicates. The final group of publications was transferred to DistillerSR, a systematic review software program that allows simultaneous analysis by multiple team members. Each publication was reviewed by 1 research assistant (KM, KO, NL, or LL). All reviewers underwent standardized training that reviewed the study inclusion criteria, the procedures for literature review, and the definitions for classifying included studies. Study eligibility criteria were predetermined based on an extensive preliminary review of the literature. Only studies performed in the United States were included in order to adequately address the question of regulation. Case studies and papers focusing on the mechanism of disease or treatment, basic science principles, or animal models were excluded as they do not necessarily provide insight into the driving forces behind increased opioid abuse in humans. Papers focused on opioids given exclusively in the hospital, such as intravenously or intrathecally, were excluded as they do not address the drivers of the abuse that occurs after discharge from the hospital, which is the focus of this review.

To ensure relevance to the orthopaedic trauma population, we included studies that described acute pain management from an orthopaedic injury. Noncancer, chronic pain management studies were also included with the recognition that the principles in treating patients suffering from chronic pain resulting from ailments such as low back pain are relevant and translatable to pain management in the orthopaedic trauma population. Papers studying specific nonmusculoskeletal injury populations, such as traumatic brain injury, or specific symptoms of disease, such as fatigue, were excluded due to their limited generalizability to most orthopaedic trauma patients. No population age restrictions were applied to the study eligibility criteria.

2.4. Categorization of literature

In order to better organize the large quantity of articles that satisfied our eligibility criteria, we further sorted the abstracts based on their relationship to 5 categories. These 5 categories were derived from Michael Porter’s Competitive Forces model, a foundational tool used to assess the competitive structure of a given industry. The model has been applied to countless industries to develop strategies to affect a given market. The 5 adapted categories used for the purposes of this study represent the major themes represented throughout opioid literature and include: consumer-focused, provider-focused, substitute-focused, industry-focused, and focus on regulatory power in the opioid industry. Articles could be sorted into more than 1 category, or could be classified as applying to “all” categories if the content provided a universal look into pain and opioid use. The goal of creating these categories is to better understand which topics or driving forces of opioid use are the best studied and which topics lack representation in the literature. The following descriptions were used to assign each paper to one or more categories (Table 2).

2.5. Substitute focused

For the purposes of this review, “substitutes” refer to an alternative product or service that provide similar benefits to a patient as opioids. In the opioid industry, there are substitutes available at every step toward chronic use, including nonsteroidal anti-inflammatory drugs (NSAIDs), nonopioid analgesics, complementary and alternative medicine (CAM), or physical therapy.

2.6. Provider focused

In the opioid industry, the providers are those involved with the development, production, and distribution of opioids. This
Table 1
Detailed search strategy for the scoping review.

| Database searched | Search terms used | No. of results (total) | No. of nonduplicates |
|-------------------|-------------------|-----------------------|----------------------|
| Medline           | (Opioid OR "Opioid-related disorders" [MeSH]) AND (orthopedics OR orthopedics OR fracture OR musculoskeletal OR trauma OR "high-energy trauma") | 2480 | 2037 |
| Medline           | (Opioid OR "Opioid-related disorders" [MeSH]) AND health-insurance | 361 | 361 |
| Medline           | (Opioid OR "Opioid-related disorders" [MeSH]) AND (pharmacists OR pharmacies OR "legislation, pharmacy" [MeSH]) | 390 | 372 |
| Medline           | (opioid OR "Opioid-related disorder" [MeSH]) AND (physician OR providers OR prescriber OR clinician) AND (education OR error OR "medical error"[MeSH] OR "medication error"[MeSH]) | 626 | 565 |
| Medline           | (Opioid or "Opioid-related disorders" [MeSH]) AND ("Social Control", "Formal") [MeSH] OR regulation AND trauma | 57 | 51 |
| Medline           | Opioid AND (trauma OR injury OR orthopedics OR orthopedics) AND ("Protocols, treatment" [MeSH] OR guidelines) | 104 | 90 |
| Medline           | "Opioid-related disorders" [MeSH] AND treatment AND trauma | 161 | 146 |
| Medline           | Opioid AND "Opioid-related disorders" [MeSH] AND treatment AND "drug development" [MeSH] OR drug-industry [MeSH] | 34 | 27 |
| Medline           | Opioid OR "Opioid-related disorders" [MeSH] AND (marketing of health services) [MeSH] OR marketing | 118 | 106 |
| Medline           | Opioid OR "Opioid-related disorders" [MeSH] AND opioid replacement OR "opioid substitution treatment" [MeSH] | 140 | 127 |
| Medline           | Opioid-related disorders AND ("Cost, Health Care" [MeSH] OR "drug costs" [MeSH]) | 36 | 27 |
| Medline           | Opioid-related disorders AND "Patient Compliance" [MeSH] AND "Attitude to Health" [MeSH] | 518 | 474 |
| Embase            | opioid OR "narcotic analgesic agent" OR "narcotic dependence" AND (orthopedics/OR injury OR fracture) AND (humans)/lim AND (english)/lim AND (abstracts)/lim AND (1996–2016)/py | 772 | 618 |
| Embase            | opioid OR "narcotic analgesic agent" OR "narcotic dependence" AND "health insurance" AND (humans)/lim AND (1996–2016)/py | 326 | 253 |
| Embase            | opioid OR "narcotic analgesic agent" OR "narcotic dependence" AND (pharmacy OR pharmacist) AND (trauma OR orthopedics OR injury) AND (humans)/lim AND (1996–2016)/py | 186 | 146 |
| Embase            | opioid OR "narcotic analgesic agent" OR "narcotic dependence" AND (physician OR provider OR prescriber OR clinician) AND (education OR error OR "medication error") AND (humans)/lim AND (1996–2016)/py | 720 | 539 |
| Embase            | opioid OR "narcotic analgesic agent" OR "narcotic dependence" AND regulation AND safety AND (humans)/lim AND (1996–2016)/py | 89 | 77 |
| Embase            | opioid OR "narcotic analgesic agent" OR "narcotic dependence" AND policy AND (trauma OR injury OR orthopedics) AND (humans)/lim AND (1996–2016)/py | 77 | 41 |
| Embase            | Opioid OR "narcotic analgesic agent" OR "narcotic dependence" AND "drug industry" AND (humans)/lim AND (1996–2016)/py | 138 | 0 |
| Embase            | opioid OR "narcotic analgesic agent/"exp OR "narcotic analgesic agent" OR "narcotic dependence/"exp OR "narcotic dependence" AND (financial AND ("management",exp OR management) OR "marketing",exp OR marketing) AND ("drug industry",exp OR "drug industry") AND ("pharmacoeconomics",exp OR pharmacoeconomics) AND (humans)/lim AND (1996–2016)/py | 129 | 112 |
| Embase            | opioid OR "narcotic analgesic agent" OR "narcotic dependence" AND patient compliance AND "medication compliance" AND (humans)/lim AND (1996–2016)/py | 62 | 53 |
| Embase            | Opioid OR "narcotic analgesic agent" OR "narcotic dependence" AND treatment AND trauma AND (humans)/lim AND (1996–2016)/py | 404 | 262 |
| PsycInfo          | Opioid AND (orthopedics* OR trauma OR injury OR fracture); 1996–present; humans | 418 | 417 |
| Guideline.gov     | "Opioids or narcotics" AND "orthopedics OR trauma OR injury OR fracture" | 71 | 68 |

Table 2
Descriptions and examples of the categories used to organize the current literature.

| Category          | Includes papers with a primary focus on:                                                                 | Examples                                                                                     |
|-------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Substitute focused| Alternative product or service that provide similar benefits to a consumer as opioids (nonopioid analgesics, ORTs, CAM, physical therapy) | "Prescription opioid and benzodiazepine use after road traffic injury,” “Extended-Release Naltrexone: A Qualitative Analysis of Barriers to Routine Use” |
| Provider focused  | Prescribers (physicians, nurse practitioner, and physician assistants), pharmacists, pharmaceutical companies | "The association of pain, stress, and anxiety measures with receiving opioid medications for the treatment of painful conditions in the ED,” “Race, ethnicity, and management of pain from long-bone fractures: A prospective study of two academic urban emergency departments” |
| Consumer focused  | Payers (includes both patients and insurance providers)                                                   | "Change in provider perspectives about opioid analgesics following a multidisciplinary educational intervention to enhance safe opioid use,” “Pain management and provider liability: no more excuses.” |
| Regulation focused| Regulation of pharmaceutical companies, prescribers, patients, insurance companies, and hospital systems by the federal or state government, licensing agencies, institutions, and individual health care professionals | “Trauma pain protocol: an interdisciplinary approach to process improvement,” “Analysis of pharmacist-provided Medication Therapy Management (MTM) services in community pharmacies over 7 years” |
| Industry focused  | Competition between different opioids currently on the market, and those publications assessing entry of new medications into the industry | “Advancement of opioid analgesia with controlled-release oxycodone,” “Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers—United States, 2002–2004 and 2008–2010” |
| Multithematic     | Every aspect of opioid use                                                                               | “Balancing the costs and benefits of opioid analgesics in the United States,” “Addressing opioid drug misuse in America,” “Causes and consequences of inadequate management of acute pain” |
includes the prescribers (physicians, nurse practitioners, and physician assistants) and the pharmacists, and the pharmaceutical companies. These groups control the industry by providing legal access through reception of a prescription, by supplying the drugs in a pharmacy, and by producing and pricing the drugs, respectively.

2.7. Consumer focused
In the opioid industry, the consumers are those concerned with the purchase, receipt, or cost of opioids. This includes the patients and the insurance providers. The opioid industry is characterized by having a very large buyer-to-provider ratio, a strong dependence on existing distribution channels, and a high level of emphasis placed on buyer satisfaction, which creates a degree of leverage for the buyers.

2.8. Regulation focused
In the opioid industry, there is potential for regulation at each level: pharmaceutical companies, prescribers, patients, insurance providers, and hospital systems. In medicine, restrictive policies arise from and can be enforced by a wide range of regulatory bodies. This includes the federal or state government, licensing agencies, institutions, insurers, and individual health care professionals. Restrictive policies can affect the opioid industry in many ways: they can help or hinder entrance of new medications or substitutes, affect the ability of providers to distribute a product, and regulate how and which buyers can use certain products.

2.9. Industry focused
We defined industry-focused papers as those publications that focused on competition between different opioids currently on the market, and those publications assessing entry of new medications into the industry. This category encompasses groups discussed above (i.e., insurance companies and pharmaceutical companies) but focuses on how these groups influence the opioid market.

2.10. Data abstraction
During the abstract screening phase, included papers were not only sorted into categories, but were also marked as either “relevant” or “extremely relevant.” Papers were deemed extremely relevant if they directly referenced the orthopaedic trauma population, or if they provided a uniquely relevant look into the driving forces behind opioid misuse. The papers marked “extremely relevant” were further reviewed qualitatively by a team of research assistants. The overarching themes were mapped and presented to a multidisciplinary team consisting of an orthopaedic surgeon (GS), a psychiatrist specializing in addiction (CW), and a clinical researcher specializing in health economics and traumatology (NO). This team worked to identify the major themes in the literature as well as potential research gaps for future investigation.

3. Results
3.1. Citation retrieval
The search strategies generated 8760 citations, out of these 2101 duplicates were removed, and an additional 3881 publications were removed during the title screening phase for failing to meeting the eligibility criteria. The abstracts of 2776 papers were reviewed for further eligibility using detailed exclusion and inclusion criteria. About 339 of these were discarded due to lack of available abstracts and another 1271 were excluded because they did not fit the eligibility criteria. The final data set was comprised of 1166 publications (Fig. 1). A total of 607 of these final abstracts were marked as “extremely relevant” (52%) and the other 559 (48%) were marked “relevant.” About 51% of the included articles were published in the past 5 years (Fig. 2).

3.2. Summary of literature
Around 36.4% of the total included articles applied to the strength of the providers (n = 425). About 25.2% of the included papers (n = 294) concerned substitutes for opioids. A total of 19.6% (n = 229) provided information on the customers in the industry, 15.7% (n = 183) focused on regulatory power in the opioid industry, 14% (n = 163) considered the industry itself, including evaluating new entrants into the industry and competitive rivalry between current players in the industry, and 11.7% (n = 137) of all 1166 included publications applied to all six categories (Fig. 3). Of the 1166 included papers, only 3 included papers with a central focus on orthopaedic trauma patients. These papers included a prospective cohort study, a systematic review, and a retrospective cohort study. There were no randomized-controlled trials concerning opioid misuse in the orthopaedic trauma population.

3.3. Substitutes
Of the 294 articles addressing the substitute theme, 133 were deemed “extremely relevant” (45.2%) by the reviewers. The sweeping majority of these papers focused on pharmaceutical opioid substitution therapies such as buprenorphine, naloxone, and methadone. A substantial proportion analyzed various procedures or treatments that reduced opioid requirements such as nerve blocks, acupuncture, and ankle aspiration. Some publications considered other pharmaceutical interventions that can be used in conjunction with opioids such as NSAIDs, benzodiazepines, and gabapentin. Few papers examined the role of complementary therapies for pain treatment.

The largest represented topic was opioid replacement therapies (ORTs). These interventions involve “replacing” an illegal or misused opioid (such as heroin or oxycodone) with a longer acting and less euphoria-producing opioid (Table 3). The most commonly prescribed ORTs in the United States are buprenorphine and methadone. In the context of the treatment of opioid use disorders, these medications are only prescribed and dispensed by certified physicians and, in the case of methadone, the patients are required to be under strict supervision. Collectively, these programs are described as Medication Assisted Therapies. Our examination of the literature produced 62 papers about buprenorphine. These papers focused on a wide and thorough range of topics such as regulation, implementation, effectiveness, education, access, prescribing practices, available formulations, safety concerns, and abuse. Methadone was another highly represented topic with 30 papers addressing the efficacy, stigma, outcomes, cost, retention, management, and safety concerns associated with methadone maintenance therapy. Authors also addressed gabapentin (3 papers) and benzodiazepines as co-prescribed interventions for the treatment of chronic pain and pain post-injury. Few publications (6 papers) discussed the use of NSAIDs as a complement or alternative to opioids. Ten papers considered the benefits of CAM, acupuncture, and talk
Records identified through database searching  
(n=8,760)  
Medline (n=5,368)  
EMBASE (n=2,903)  
PsycINFO (n=418)  
Guidelines.gov (n=71)  

Records after duplicates removed  
(n=2,101)  

Records screened  
(n=6,659)  

Records excluded  
(n=3,881)  

Abstracts assessed for eligibility  
(n=2,776)  

Abstracts excluded, with reasons  
(n=1,610)  
No abstract, non-US, case reports, pre-1996,  
duplicate, basic science, ineligible population,  
excluded disease category  

Studies included in scoping review  
(n=1,166)  

Extremely Relevant  
(n=607)  

Relevant  
(n=559)  

Figure 1. Flow diagram.
therapy. A significant number of papers analyzed the effectiveness of using a specific procedure or analgesic such as a nerve block in order to reduce opioid use at discharge.

### 3.4. Providers

A total of 236 of the 425 provider-focused papers (55.5%) were considered “extremely relevant” by the reviewers. The vast majority of these papers focused on the role of the prescriber, typically physicians. Thirty-five papers focused on the role of pharmacists in the distribution and monitoring of opioid prescriptions. There were only three papers that focused directly on the role of pharmaceutical companies in the opioid industry.

Many papers that focused on the prescribers evaluated prescribing practices, especially those employed to treat postfracture pain in the emergency departments and chronic pain in ambulatory clinics. Additionally, there is a large focus in the literature on analyzing the efficacy of previously established physician guidelines for managing traumatic injury or chronic pain. This includes papers detailing successful trauma pain protocols and effective post-operative pain management protocols. Other prescriber-focused papers focused on physician education initiatives. The articles analyzing the power of pharmacists in the opioid industry focused on prescription drug monitoring programs, the role of pharmacists in dispensing buprenorphine, and collaboration between pharmacists and physicians. Two of the papers concerning pharmaceutical companies focused on the physician–pharma relationship, and the remaining paper examined the economics of substitution therapy from a pharmaceutical perspective.

### 3.5. Consumers

Around 229 papers (19.6%) focused on the power of the buyer, 99 of these papers (43.2%) were considered “extremely relevant” by the reviewers. The majority of these papers focused on the patient. There were only five papers that focused on the role of insurance companies as “consumers” in the opioid industry.

The vast majority of consumer-focused papers concerned patients rather than insurance companies. A large number of these papers focused on how different patient characteristics such as race, gender, age, education status, injury, and self-reported pain intensity influenced opioid prescribing trends, typically in the emergency department after acute injuries. Another popular topic included patient risk factors for probable opioid misuse. There was a notable focus on patient satisfaction, pain as a medical condition (“the fifth vital sign”), and drug-seeking behaviors. There were very few publications considering patient education initiatives such as patient contracts. The limited publications concerning insurance companies compared patients on different insurance plans or analyzed the insurance status of patients. There was only one paper that focused on the insurance industry’s role in the opioid crisis.

### 3.6. Regulations/restrictive policies

Around 86 of the 183 papers that focused on the power of regulations were considered “extremely relevant” (47%). The
The majority of these papers considered regulations and protocols that could affect physicians in order to make opioid prescribing a safer enterprise. There was also a notable focus on the restriction of opioid use through intervention at the pharmacy level. Our search produced no articles analyzing regulation of pharmaceutical companies or insurance companies.

Most of the regulation-focused papers assessed policies that would directly affect physicians. Fourteen of these papers analyzed the regulations placed on prescribing substitution therapies. Fourteen papers addressed physician education as a tool for reducing nontherapeutic opioid use. There was a large focus on implementing prescribing protocols and best practice guidelines for opioids at different levels of care, including in ambulatory clinics, emergency departments, and operating rooms. Seven papers discussed the implementation of opioid risk evaluation and mitigation strategies, including the FDA-approved risk evaluation and mitigation strategies for extended-release and long-acting opioids. Other topics included establishment of opioid review committees, standardization of multidimensional pain scales, creation of a pain care quality extraction tool, and patient-provider agreements. The role of regulation at the pharmacy level was also well represented in the literature; 12 papers examined the efficacy and importance of prescription monitoring programs.

### 3.7. Industry

The industry theme had the fewest number of papers (14%). About 83 of the 163 manuscripts were considered “extremely relevant” by the reviewers. The majority of these papers discussed differences in efficacy of FDA-approved opioid medications in trauma-related procedures and pain treatment. Other topics included: comparing extended versus controlled release medications, comparing time scheduled vs. pain contingent dosing, comparing methods of delivery (such as transdermal, intranasal, or buccal), and evaluating existing tamper-resistant or harm-reducing formulas. Surprisingly, only 2 papers analyzed the transition from prescription opioid use to the illicit use of heroin. Many papers focused on the implementation of new drugs such as nociception/orphanin FQ and ziconotide. A significant number of papers also examined the implementation of new medication and analyzed the efficacy as compared to the original. For example, 1 study compared the rate of abuse of a reformulated therapy to that of the original drug. Fourteen papers also considered the barriers to implementing new substitution therapies. Six papers discussed the efficacy of abuse deterrent technology at reducing opioid abuse. Only 1 paper considered novel off-label use of an opioid.

### 4. Discussion

The findings of this study define areas of research attention and knowledge gaps in the literature relevant to opioid use and misuse among orthopaedic trauma patients (Fig. 4). Utilizing the novel scoping review technique allowed for the organization of the literature into five categories that directed the synthesis. More than 60% of the overall publications focused on either opioid

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Schematic representation of major topics within each category. This figure highlights the different opioid-related topics identified in the literature organized into the 5 themes. The topics are further divided by whether they contribute to the opioid epidemic (green upward arrow) or whether they are intended to address problems associated with the opioid epidemic (red arrow). Further, in gray are themes that were identified by our narrative review to be missing from the literature.
providers (mainly physicians) or opioid substitutes (mainly ORTs). Very few of the identified publications studied the role of insurance providers or pharmaceutical firms and their involvement in opioid abuse and long-term nontherapeutic use. In line with the Centers for Disease Control and Prevention’s (CDC) contention that, “long-term opioid use often begins with treatment of acute pain,”[11] this study delineates previous academic investigation into possible drivers of the opioid epidemic emanating from an acute injury.

In Figure 4, the green upward arrows represent factors that increase opioid use and the red downward arrows represent factors that decrease, or have the potential to decrease, opioid use. The topics in gray font were not represented in the literature included in this scoping review.

Of the 1166 papers included in the study, 52% of these papers were marked as “extremely relevant” to our expanded research question. However, only 3 papers specifically focused on the orthopaedic trauma population. The majority of papers concerned either opioid providers (36.4%) or various substitutions for opioids (25.2%). There were few papers evaluating pharmacological or other therapeutic substitutes for trauma patients at the time of injury and a notable lack of papers concerning the involvement of pharmaceutical companies or insurance companies in opioid overuse relevant to trauma patients. The study has identified a knowledge gap pertaining to evaluating the transition from prescription opioid use to illicit heroin use among those patients with orthopaedic injury. Finally, we found limited investigation comparing the efficacy of various opioid medications in the treatment of acute post-traumatic pain.

Our use of the scoping review method allowed this study to address a broad topic with limited and unsystematic representation in scientific literature. The malleable nature of the scoping review method created the unique opportunity to seek resources in non-peer-reviewed journals, such as state guidelines, and allowed us to adjust our methods based on what was available. Despite this flexibility, we applied rigorous standards to our searches and screening, including verifying the strength of our search strategies, methodologies, and eligibility criteria with a health sciences research librarian. We also trained all 4 reviewers systematically and created an additional review system for papers whose relevance was not immediately apparent. Overall, the benefit of the scoping review is reflected in our ability to sort a large number of papers into digestible categories, which could then be evaluated in order to inform interested entities about the state of the field.

Our collaboration with experts on this topic allowed us to identify themes not represented in the literature, but prevalent in the field. We consulted a psychiatrist specializing in addiction, a doctor of social work specializing in opiates, and a healthcare business professor. Each of these individuals spoke of their experience treating patients with opioid addiction or studying opioid addiction and the surrounding industry. After being presented with the results of our searches, they identified key topics that seemed underrepresented in the literature but were highly pervasive in practice. Additionally, they each elaborated on the limitations of using a rigorous study design to examine a highly complex and fast-changing field, discussed in detail below.

We made several important observations about the content of the existing literature. The most widely discussed topic was ORTs within the category of “substitutions.” Generally considered as a viable therapeutic option for the treatment of severe opioid dependence, the safety and efficacy of ORTs remain unclear and requires more study. Another strongly represented topic was the control of physician involvement in opioid distribution, within the category of “provider-focused” papers. This was approached from various angles, such as physician education and implementation of prescribing guidelines. It is imperative to further investigate the willingness of physicians to engage in the types of programs implemented at select institutions in order to evaluate the potential impact of these programs.

The “regulations and restrictions” category, comprising 15.7% of the papers, represented perhaps the widest range of topics within a single category. Publications offered examples of regulation of every facet of the opioid industry, including physicians, pharmacists, and substitution therapies. Although most papers examined individual restrictions (e.g., a single prescription monitoring program or a particular physician education initiative), it would be interesting to evaluate the implementation of multiple regulatory interventions at an institution or within a medical system.

The papers sorted into the “consumer-focused” category focused mainly on various qualities of patients. This ranged from analyzing characteristics that predisposed patients to abuse (such as prior use of opioids) to analyzing characteristics that dictate how much and what types of medications are received (such as time of injury, gender, and race). There were also a number of papers evaluating patient satisfaction as a driver of opioid prescribing practices. This information exposes an opportunity for improvement within the industry: opioid prescriptions should reflect pain and extent of injury, rather than race, gender, or day of the week the injury occurred. Furthermore, the emphasis on pain and the evaluation of pain severity needs to be better standardized.

In contrast to those topics that were highly represented, there were many important facets of the opioid industry and various drivers of abuse that were absent from the literature. These topics had been identified by a separate narrative review and with the help of our expert collaborators (Table 4). To begin, there were only 3 papers that discussed the involvement of the pharmaceutical industry on the opioid epidemic. As evidenced by journalistic publications and various historical exposés on the opioid epidemic, the pharmaceutical industry has played an enormous role in establishing and maintaining opioids as a cornerstone of our pain treatment protocols. For instance, in a recent Washington Post article,[12] the $10 billion industry is evaluated for its growth potential, specifically the emergence of a subindustry involving treatment of secondary effects. A physician interviewed for the article states, “The pharmaceutical industry

| Knowledge gap | Theme |
|---------------|-------|
| Use of nonopioid analgesics for acute pain | Substitution focused |
| Patient education about opioid medications | Consumer focused |
| Physician education about prescribing opioid medications | Consumer focused |
| Insurance providers effects on opioid prescribing | Consumer focused |
| Marketing of opioids by manufacturers | Industry focused |
| Government restrictions on entry/exit of opioid medications into the marketplace | Industry focused |

Table 4: A summary of topics that are known to drive the opioid epidemic but are not represented in the scientific literature reviewed here.
literally created the problem [of opioid induced constipation]. They named it, and they started advertising what a serious issue it is. And now they’ve got the solution for it.” Despite the widely accepted role played by pharmaceuticals, little peer-reviewed research has been performed on the topics of marketing, questionable R&D methods, distribution, or dissemination of misinformation.

The insurance industry is also under-examined in peer-reviewed literature. The projected cost of opioids to United States insurance companies is $72.5 billion per year.[13] In contrast to pharmaceutical firms, insurance providers are economically disadvantaged by the opioid industry and sub-industries. Insurance providers also have the tools to establish ubiquitous prescription monitoring programs in order to monitor high risk patients. Furthermore, insurance agencies may have the ability to dictate which opioids or ORTs are covered by insurance, effectively manipulating prescribing practices. Despite the potential influence, there were no peer-reviewed publications on these topics.

There were also few papers discussing alternative medications. As mentioned, the majority of the “substitute-focused” papers concerned medication-assisted therapies to replace opioids after the transition to addiction has already occurred. There were minimal publications considering the use of alternate pharmaceuticals (such as NSAIDs) or interventions (such as physical therapy) for traumatic pain at time of injury. This was also the case for complementary medical techniques such as acupuncture. Research suggests that NSAIDs may offer the same pain relief at a lower cost for some patients.[14] Finally, there was a gap in the literature concerning the optimum length of opioid prescription time post-injury. The CDC currently recommends 3 to 7 days of opioids for an acute injury. ER/LA opioids are not recommended to treat traumatic injury pain.[15] Despite these short-term recommendations, 27% of patients prescribed an opioid on a short term basis ended up taking them considerably longer.[16] This topic or the efficacy of these recommendations was not examined in the peer-reviewed literature.

Throughout the search and screening process, we identified various limitations of the methodology and the literature itself. We were advised on further limitations after consultation with experts in the field. To begin, our search was performed in late June 2016. Because of the rapid expansion of publications concerning opioids, the results do not reflect even more recent publications which may already fill some of the voids we have identified. Another limitation concerns the nature of government restrictive bodies. The CDC, FDA, DEA and other government organizations are not compelled to publish relevant information concerning controlled substances in the scientific literature, and as such, a literature search may miss information that is simply posted on agency websites or through non-peer-reviewed publications.

Additionally, the scientific community is limited by the nature of the opioid industry itself. It is difficult to quantify certain aspects of opioid use, for example, transition from therapeutic to nontherapeutic use, abuse of substitute therapies, prescription opioid diversion, length of use (as patients can seek the drugs elsewhere), and transition to use of illegal substances such as heroin. Lastly, a huge limitation was realized early during the searching process. The lack of publications concerning opioids and orthopaedic trauma (or trauma in general) required us to expand our search to include papers focused on the general population’s use of opioid medications. While this enabled us to better describe the opioid industry’s literature representation, it diluted the focus on post-injury opioid use.

5. Conclusions

The results of the current study provide a detailed summary of the available literature concerning opioid use relevant to orthopaedic trauma patients. The strengths and weaknesses identified provide plausible suggestions for future research projects. Using the results from this study, we will assess orthopaedic surgeons’ opinions and knowledge about the themes identified in the literature, such as physician education and various restrictive policies. Additionally, multiple opportunities to perform systematic reviews on topics that have been widely represented, such as ORTs, PMPs, or prescribing guidelines, have been identified. Finally, we have recognized multiple areas in which there is a blatant lack of peer-reviewed information, which can be addressed by the orthopaedic community (Table 5). The summaries from this paper will be used in future discussions between physicians, public health workers, and addiction specialists as we pursue interventions aimed at reducing long-term opioid misuse among orthopaedic injury patients.

References

1. Mularski RA, White-Chu F, Overbay D, et al. Measuring pain as the 5th vital sign does not improve quality of pain management. J Gen Intern Med 2006; 21:607–612.
2. Ling W, Mooney L, Hillhouse M. Prescription opioid abuse, pain and addiction: clinical issues and implications. Drug Alcohol Rev 2011; 30:300–305.
3. Friedman R. Increased scrutiny of medical providers: a cause for reflection and diligence. Pain Practitioner 2010; 20:26–33.
4. Morris BJ, Mir HR. The opioid epidemic: impact on orthopaedic surgery. J Am Acad Orthop Surg 2015; 23:267–271.
5. Bjur PE, Bérand A, Esses D, et al. Lack of influence of patient self-report of pain intensity on administration of opioids for suspected long-bone fractures. J Pain 2006; 7:438–444.
6. Holman JE, Stoddard GJ, Higgins TF. Rates of prescription opiate use before and after injury in patients with orthopaedic trauma and the risk factors for prolonged opiate use. *J Bone Joint Surg Am* 2013; 95:1075–1080.

7. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician* 2008; 11 (2 suppl):S105–S120.

8. Levac D, Colquhoun H, O’Brien KK. Scoping studies: advancing the methodology. *Implement Sci* 2010; 5:69.

9. Arksey H, O’Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol* 2005; 8:19–32.

10. Porter ME. The five competitive forces that shape strategy. *Harv Bus Rev* 2008; 86:25–40.

11. Centers for Disease Control and Prevention. Guidelines for Prescribing Opioids for Chronic Pain. Available at: https://www.cdc.gov/drugoverdose/pdf/guidelines_factsheet-a.pdf. Accessed August 29, 2016.

12. Cha AE. The drug industry’s answer to opioid addiction: More pills. *The Washington Post*. 16 Oct 2016. Available at: https://www.washingtonpost.com/national/the-drug-industries-answer-to-opioid-addiction-more-pills/2016/10/15/181a529c-8ae4-11e6-bf60-d53h592i176c_story.html?utm_term=.ac98eb27626. Accessed October 26, 2016.

13. Katz NP, Birnbaum H, Brennan MJ, et al. Prescription opioid abuse: challenges and opportunities for payers. *Am J Manag Care* 2013; 19:295–302.

14. National Safety Council. NSAIDs are stronger pain medications than opioids: A Summary of Evidence. Available at: http://www.nsc.org/RxDrugOverdoseDocuments/evidence-summary-NSAIDs-are-stronger-pain-medications-than-opioids-with-IFP.pdf. Accessed August 14, 2016.

15. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep* 2016; 65:1–49.

16. Hooten WM, St Sauver JL, McGree ME, et al. Incidence and risk factors for progression from short-term to episodic or long-term opioid prescribing: a population-based study. *Mayo Clin Proc* 2015; 90:850–856.