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PRESCRIPTION OF OPIOIDS TO YOUTH 2005-2016: AN EXAMINATION OF TRENDS, PATIENT CHARACTERISTICS, AND OUTCOMES THROUGH 12 MONTHS

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BY

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B.S., Art Therapy, Lesley University, 2010
M.A., Clinical Mental Health Counseling, 2012

DISSERTATION

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DEDICATION

This work is dedicated to the youth in New Mexico who lost their lives to complications related to opioids, and to their families and loved ones who carry that emptiness with them every day. We need to do better and we will.

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I am incredibly blessed to have had phenomenal mentorship and support throughout my early career development. Completion of this dissertation and doctoral degree reflects the culmination of these years of support and guidance from folks who invested in me and believed in my potential to make a meaningful contribution to this field, particularly Dr. Kevin E. Vowles, Dr. Laura E. Simons, Dr. Christine B. Sieberg, Dr. Ronald Kulich, and Dr. Sara J. Becker. This study was generously funded by the Center for Regional Studies at the University of New Mexico. Its development and successful execution was made possible with the expertise of Dr. Vowles, Witkiewitz, Palermo, Rivers, and Groenewald, as well as the skillful data extraction services of the Clinical and Translational Science Center at the University of New Mexico Hospital.

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ABSTRACT

Data on all outpatient opioid prescriptions (*N*=71,647) to youth below age 21 (*N*=42,020) from 2005-2016 were extracted from electronic medical records within a university hospital system, including demographic characteristics, markers of morbidity, and mortality. Relative risk was calculated for markers of morbidity and mortality based on sociodemographic characteristics. The sample was primarily male (55.0%), Hispanic/Latino (50.1%), English-speaking (88.9%), and publicly insured(50.1%). Mean age was 13.54 (*sd* = 6.50). From 2005-2016, overall frequency of opioid prescriptions increased by 86.6% (from 2470 to 4610) with the largest increase (206.2%) observed from 2005-2008 (2470 to 7562). Patients who were older, White, and Non-Hispanic were more likely to receive multiple opioid prescriptions. Large increases in opioid-related morbidity and mortality were documented, although base-rates remained low. Significantly increased risk of adverse outcomes was observed in patients receiving multiple opioid prescriptions, and in patients who were older, of minority race, and publicly insured or uninsured.

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Chapter 1

Introduction

Problematic opioid use and subsequent adverse consequences, including opioid-related overdose deaths, are well-documented public health concerns in the United States (US). These concerns are partially fueled by the dramatic increase in rates of opioid prescriptions and community availability of prescription opioids over recent decades (Manchikanti, Fellows, Ailinani, & Pampati, 2010; Shaheed, Maher, Williams, Day, & Mclachlan, 2016; Vowles et al., 2015). In adults, drug overdose is the leading cause of accidental death, whereby 60-70% of prescription drug overdose deaths can be accounted for by prescribed opioids (Centers for Disease Control and Prevention National Center for Health Statistics, 2015; Jones, Mack, & Paulozzi, 2013; Rudd, Aleshire, Zibbell, & Gladden, 2016; Vowles et al., 2015) and opioid-related overdose deaths are decreasing the life expectancy of Americans (Kochanek, Murphy, Xu, & Arias, 2017). Further, opioid misuse, defined as "opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects" (Vowles et al., 2015, p. 570) is associated with increased heroin use (Carlson, Nahhas, Martins, & Daniulaityte, 2016) among other adverse consequences (e.g. overdose).

While these issues are relatively well characterized in adults, opioid prescribing trends and implications remain unclear in children, adolescents, and young adults (Schechter, 2014). Results from published national studies examining opioid prescribing rates to youth in the last two decades vary greatly, with some data indicating little to no significant change (Groenewald, Rabbitts, Gebert, & Palermo, 2015), while others report increases of 40%-100% (Fortuna, Robbins, Caiola, Joynt, & Halterman, 2010; Mazer-

Amirshahi, Mullins, Rasooly, van den Anker, & Pines, 2014; Sheridan et al., 2016). Nonetheless, opioids are a part of standard treatment for painful conditions in youth, such as traumatic injuries, post-surgical pain management, cancer, and dental care (Groenewald et al., 2015; Walco, Gove, Phillips, & Weisman, 2017).

Although prescription trends in youth are uncertain, two things are clear; both of which shadow trends in adults: 1) youth are misusing opioids, and 2) problematic opioid use among youth is associated with substantial risk of morbidity and mortality. In 2016, 1.7% of persons age 12 or older initiated illicit drug use with pain relievers, which was more than initiation rates of all other illicit drugs, aside from marijuana (Substance Abuse and Mental Health Services Administration, 2017). Findings from the 2015 National Survey on Drug Use and Health revealed that pain relievers, typically opioids, were the most widely used psychotherapeutic drug among persons above the age of 12 (Center for Behavioral Health Statistics and Quality, 2016), with leftover prescriptions repeatedly identified as a primary source for nonmedical use (Binswanger & Glanz, 2015; McCabe, West, & Boyd, 2013a; Voepel-Lewis, Wagner, & Tait, 2015). More specifically, in 2016, approximately 3.6% of adolescents (n~891,000 age 12 to 17 years) and 7.3% of young adults (n=~2.5 million age 18 to 25) reported current misuse of prescription pain relievers. Further, it is estimated that .6% of adolescents and 1.1% of young adults had an opioid use disorder in 2016 (Substance Abuse and Mental Health Services Administration, 2017).

Nonmedical use of prescription opioids in childhood has also been identified as a strong predictor of initiating heroin use during adolescence (Cerdá, Santaella, Marshall, Kim, & Martins, 2015; Palamar, Shearston, Dawson, Mateu-Gelabert, & Ompad, 2016). Of greater concern, deaths from prescription drug overdoses in youth doubled from 2001

to 2014 (Center for Disease Control & National Center for Health Statistics, 2015), as did inpatient admissions due to opioid poisoning from 1997 to 2012 (Gaither, Leventhal, Ryan, & Camenga, 2016). In 2015, drug-related death rates for youth age 15-19 in the United States was highest for opioids, especially heroin (Curtain, Tejada-Vera, & Warner, 2017). Recent data also reflect an association between national rates of opioid prescribing to adolescents and rates of adolescent calls to poison centers regarding opioid ingestions (Sheridan et al., 2016).

Further, evidence has shown that adolescents tend to underestimate the potential risk of taking prescription opioids (Martin, Bhalla, Beltran, Veneziano, & Tobias, 2014), with one study reporting that 41% of adolescents perceived prescription drugs to be safer than illegal drugs and almost a third (29%) believed that prescription pain relievers were not addictive (Martin et al., 2014). Finally, exposure to opioids as an adolescent appears to present a risk for problematic opioid use as an adult. A longitudinal study, using data from the Centers for Disease Control (CDC) Monitoring the Future study (The Regents of the University of Michigan, 2016), found a significant association between both medical *and* nonmedical use of prescription opioids during adolescence and subsequent non-medical use of opioids when participants were 35 years of age (McCabe, Veliz, & Schulenberg, 2016). Additional work in this area found that adolescents who self-reported medical and nonmedical opioid use were more likely to engage in medical use *before* nonmedical use (McCabe et al., 2017). In other words, *any* exposure to opioids (e.g. medical or non-medical) during adolescence may carry with it potential for short and long-term risk.

Individual Factors Associated with Receiving an Opioid Prescription Before Age 21

Two other key areas lack clarity in relation to patterns of pediatric opioid prescribing. First is identification of what individual factors are associated with receipt of an opioid prescription as a young person. Some available data suggests that ethnic minority youth are *less* likely to receive an opioid for pain (Groenewald et al., 2015; Pletcher, Kertesz, Kohn, & Gonzales, 2008; Sadhasivam et al., 2012; Wu, Woody, Yang, Pan, & Blazer, 2011), despite reporting pain of greater intensities than Caucasian youth (Pletcher et al., 2008; Sadhasivam et al., 2012; Wu et al., 2011). Other data indicates that youth who are older (Groenewald et al., 2015), have a preexisting mental health diagnosis (Richardson et al., 2012; Welsh et al., 2017), or multiple pain complaints (Richardson et al., 2011) are *more* likely to receive an opioid or misuse opioids. Overall, the influence of other potentially important demographic and health-related variables requires further examination. It is also perplexing that although the prevalence of chronic pain is higher in female youth (King et al., 2011), research has not found significant differences in opioid prescribing rates to youth based on sex. In terms of misuse, however, one recent study with a non-clinical population did find that more males than females reported non-medical opioid use (Osborne, Serdarevic, Crooke, Striley, & Cottler, 2017) and national rates of drug overdose death rates for males age 15-19 were higher than that of females (Curtain et al., 2017).

Additionally, to our knowledge, there are no data available investigating how aspects of opioid dose or prescription frequency may influence health-related outcomes in youth. Specifically, there is a need to examine demographic and health-related factors in relation to the number of opioid prescriptions received (i.e., single versus multiple) and whether number of opioid prescriptions is associated with more problematic outcomes. This knowledge gap is significant because it is documented that opioid dependence and

withdrawal symptoms can be identified in children prescribed opioids after as little as seven days (Galinkin & Koh, 2014). Further, chronic opioid use (receipt of 3 or more prescriptions [Chou, Fanciullo, Fine, Adler, et al., 2009; Chou, Fanciullo, Fine, Miaskowski, et al., 2009; Portenoy, 1996]) in adults is associated with greater distress and disability, more frequent opioid misuse, and may be a risk factor in progression to heroin use (Chou, Fanciullo, Fine, Adler, et al., 2009; Dowell, Haegerich, & Chou, 2016; Højsted, Nielsen, Guldstrand, Frich, & Sjøgren, 2010; Kobus et al., 2012; Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014).

Opioid Prescribing in a High-risk, Diverse state

Opioid prescribing rates and overdose death rates vary significantly between states (Center for Disease Control, 2016; Centers for Disease Control and Prevention, 2014). The State of New Mexico (NM) consistently has one of the highest rates of drug-induced deaths, with 24.7 deaths per 100,000 people in 2015, 82% of which involved prescription opioids or heroin (New Mexico Department of Health, 2017). In NM youth, who comprise over one quarter of the state population (United States Census Bureau, 2016), prescription opioids are the second most commonly used drug behind marijuana, with prevalence highest among males and those who identify as American Indian (Substance Abuse Epidemiology Section New Mexico Department of Health, 2016). From 2000 to 2014, overdose deaths in NM youth aged 0 to 24 years, largely from opioids, accounted for 8.5% of all overdose deaths in the state (Substance Abuse Epidemiology Section New Mexico Department of Health, 2016). In Albuquerque, the state's largest city, a recent city-wide needs assessment of changes in opioid use and treatment availability reflected an increase in both nonmedical opioid use and in youth seeking treatment for problematic opioid use (Greenfield, Owens, & Ley, 2014).

Treatment agencies interviewed for this needs assessment shared clinical observations that youth, particularly those with chronic pain, are initiating use with prescriptions opioids and eventually switching to heroin to save money.

Opioid Prescribing Practices in Pediatrics

In 2015, the U.S. Food and Drug Association (FDA) approved the use of an opioid, OxyContin, for non-cancer pain treatment in pediatric patients age 11 to 16 years (U.S. Food and Drug Administration, 2015). Several sets of published guidelines exist for administration of opioids for chronic non-cancer pain treatment in adults (American Academy of Pain Medicine, American Pain Society, & American Society of Addiction Medicine, 2004; Chou, Fanciullo, Fine, Adler, et al., 2009; Costello, 2015; Dowell et al., 2016), but there is a dearth of clear guidelines specifically for using opioids with youth. Delineating opioid prescription patterns in youth from preexisting data can illuminate areas of inconsistency, inequality, or inappropriate prescribing that may be useful in the development of pediatric opioid prescription guidelines which incorporate the dual goals of improving patient outcomes and minimizing risks of adverse consequences.

The Current Study

For the current study, data were extracted from the University of New Mexico Hospital (UNMH) medical records system for all youth age 21 and under who received at least one outpatient opioid prescription between January 2005 and December 2016. The primary aim was to quantify trends in prescription of opioids to youth from 2005 to 2016 in NM based on year, demographic, and medical variables. The secondary aims were to: 1) identify individual factors associated with receipt of single or multiple prescriptions, and 2) examine outcomes following last opioid prescription, including markers of morbidity (e.g. receipt of a prescription for medication-assisted treatment) and mortality,

as well as identification of individual and medication characteristics associated with increased risk of experiencing an adverse outcome.

It was hypothesized that rate of opioid prescriptions to youth in NM would significantly increase from 2005 to 2016, and that differences in prescribing rates would be observed based on demographic (e.g. sex, ethnicity) and clinical (e.g. diagnosis) characteristics, consistent with the published literature. Regarding Aim 2, it was further hypothesized that only a small proportion of youth would receive more than one opioid prescription and that, consistent with the extant literature regarding differences in prescribing rates based on ethnicity, non-Hispanic Whites would be more likely to receive multiple opioid prescriptions in comparison to members of racial/ ethnic minority groups (Groenewald et al., 2015). Finally, based on trends in the adult literature (Hooten, St Sauver, McGree, Jacobson, & Warner, 2015), it was hypothesized that receipt of repeat or multiple prescriptions would be associated with increased rates of morbidity and mortality relative to single prescriptions.

Chapter 2

Methodology

Setting and Data Source

Pre-existing data was extracted from the electronic medical records system at the University of New Mexico Hospital (UNMH). The hospital is located in an urban area, serves as New Mexico's only Level 1 trauma center, and is the primary site of pediatric specialty care. Data were extracted and de-identified using the services of the UNMH's Clinical Translational Science Center (CTSC). The CTSC team acts as an "honest broker" to evaluate patients in relation to stated inclusion criteria, extract the requested variables from the electronic health record (EHR), and de-identify patient health information (PHI) to safeguard confidentiality. The UNMH EHR was established in 2005, thus, data extraction dates were from January 1, 2005 to December 31, 2016.

Institutional Review Board approval was obtained to perform the data extraction and planned analyses detailed below. The study was deemed "Exempt" as data were pre-existing and de-identified (Study approval ID: 16-123).

Measures

Inclusion criteria along with extracted variables in the dataset are presented in **Table 1** and summarized below. Only encounters with opioid prescription dates within the study time frame were extracted and included.

Sample included patients age 0 to 21 years who received an outpatient prescription for an opioid between 2005 and 2016. Inpatient opioid prescriptions were excluded.

Individual/ baseline demographic factors include relevant descriptive medical and psychosocial characteristics. These included age at first prescription encounter, race, ethnicity, and insurance payer status.

Opioid prescription variables were extracted for each outpatient visit where an opioid was prescribed in order to characterize aspects of the prescription and encounter (e.g. encounter location, active diagnoses). Type of opioid prescription was classified based on the active opioid agonist agent (e.g. oxycodone and acetaminophen/oxycodone were both classified as "oxycodone"): Oxycodone, Hydrocodone, Codeine, Tramadol, Morphine, Fentanyl, and Other (i.e. meperidine, opium products). Prescriptions for opioid antagonists (e.g., Methadone, Suboxone) were excluded, as they can be used for pain management or medication-assisted treatment of an opioid use disorder and medication indication was not always inferable from the data. A total of 99 individuals in the dataset received prescriptions for both an opioid agonist and an antagonist.

The total number of opioid prescriptions received by each individual during each year of the data extraction period and over the course of the study timeframe was tallied to derive the total number of prescriptions. Furthermore, a binary variable was created to denote if individuals received single or multiple opioid prescriptions over the study period.

Outcomes variables were defined as markers of morbidity (overdose, receipt of a prescription for medication-assisted treatment) and mortality.

Variable Extraction and Coding Methodology

Each case was assigned a unique ID number (in order to link patients across multiple encounters) and each prescription encounter was also assigned a unique ID by the CTSC. Frequency of opioid prescriptions across the study time frame was calculated for each patient into a "total opioid prescriptions" variable. A binary variable denoting individuals who received single versus multiple opioid prescriptions was also created. Patient age at first opioid prescription was calculated in years. Age at baseline was categorized into early childhood (0-5 years), school age (6-11 years), adolescent (12-17 years), and young adult (18-21 years). Encounter location was coded as outpatient, emergency, discharge from inpatient, or day surgery. Insurance payer status was coded into three categories: Private/ Commercial, Public/ Government Assistance (e.g. Medicaid), and Uninsured.

To examine outcomes following the patient's most recent opioid prescription encounter, patients were tracked one year after their last opioid prescription. At each subsequent encounter, we looked for evidence of a prescription for medication-assisted treatment (MAT; i.e. suboxone) as a proxy for potential development of opioid dependency. The overdose and mortality variables were extracted from the patient's entire medical history after receipt of an opioid. Additional descriptive variables were extracted for each overdose encounter, including documented substances at overdose and total number of overdoses.

Diagnoses from encounters occurring on October 1, 2015 and later utilized ICD-10 codes, due to a hospital wide transition; diagnoses from encounters prior to that date utilized ICD-9 codes. To integrate ICD-9 and ICD-10 diagnoses, coding of ICD-10 chapters and subchapters was based on ICD-9 chapters and subchapters (as the majority

of cases had ICD-9 diagnosis), such that each ICD-10 diagnosis was grouped into the related ICD-9 chapter/ subchapter.

Statistical Analysis Plan

Database merging, cleaning, and coding, was conducted using Excel and R (R Core Team, 2014) and analyses were conducted using SPSS v25 (IBM Corp. Released, 2015). Descriptive statistics and frequencies were calculated for all sociodemographic, medical, medication, and outcome variables. Frequencies across time were calculated for opioid prescriptions, individuals receiving single versus multiple prescriptions, and markers of opioid-related morbidity and mortality. Relative risk, including 95% confidence intervals, was calculated for receipt of single versus multiple prescriptions, as well as markers of morbidity and mortality based on individual sociodemographic characteristics

Chapter 3

Results

From 2005-2016, 42,020 unique patients age 21 or younger received a total of 71,647 opioid prescriptions. **Table 2** provides an overview of annual frequency of opioid prescriptions as well as number of patients receiving single or multiple opioid prescriptions.

Medication and Demographic Characteristics at Receipt of First Opioid (baseline)

Medication Characteristics. The highest number of individuals received their first opioid prescription in 2008 (n=4,439), in contrast to 2005 when only 1,733 youth received an opioid prescription for the first time (see **Table 3**). Type of first opioid prescription was most commonly Oxycodone (46.0%, n=19,318) or Hydrocodone (36.5%, n=15,331), while few (<.1%, n=16) received Fentanyl as a first opioid prescription. We were unable to calculate Morphine Equivalent Dose (MED) for each prescription, as only a very small percentage of prescriptions (<20%) had adequate dosing information to calculate MED.

Demographic characteristics. See **Table 3** for demographic characteristics of patients. Mean age at receipt of first opioid prescription was 13.52 (*sd* = 6.50), although 38.9% (n=16,327) of patients were young adults (age 18-21 years) at the time of their first prescription. The sample was primarily male (55.0%, n=23,093), of Hispanic/Latino ethnicity (50.1%, n=21,044), and most commonly reported races were White (48.3%, n=19,985) and American Indian/Alaskan Native (11.0%, 4,553), although 27.1% (n=11,241) of the sample declined to report their race or it was missing from the medical record. Patient primary language was English for most (88.9%, n=37,343), followed by

Spanish (8.9%, n=3,755). Half of the sample had public or government assisted health insurance (e.g., Medicaid; 50.1%, n=21,027).

Encounter location. Location of first prescription encounter was most commonly in the emergency department (35.6%, n=14,954) or at discharge from inpatient care (29.4%, n=12,364). Opioid prescriptions were least likely to be prescribed in an outpatient clinic encounter (12.9%, n=5,401).

Total opioid prescriptions. The majority of youth (68.80%, n=28,911) received only one opioid prescription during the study time frame, while 13,109 (31.20%) received two or more opioid prescriptions (see **Table 3).** Of the patients who received multiple prescriptions, most received two (56.91%, n=7,460), but a marked 22.2% (n=2,915) received 4 or more opioid prescriptions.

Non-opioid medications. Regarding other potentially interacting prescription drugs that were prescribed concurrently with the first opioid prescription, Benzodiazepines and Muscle Relaxants were most common, with 3.5% of the sample (n= 1465) who had an active prescription for Benzodiazepines, 1.5% prescribed Muscle Relaxants (n=618), and 0.4% prescribed an SSRI or SNRI (n=163). Individuals were rarely also prescribed anticonvulsants, tricyclic anti-depressants, or barbiturates (< .1%).

Presenting diagnoses. On average patients had 5.06 (*sd* = 5.41; range 1-64) presenting diagnoses tied to the encounter where the first opioid prescription was given; thus, baseline diagnoses are not mutually exclusive (see **Table 4**). Diagnoses were most frequently from the ICD-9 chapters for "Injury and Poisoning" (most common diagnoses in this chapter were 'fractures') and "Supplementary Classification Of External Causes Of Injury And Poisoning'" chapters (most common diagnosis was 'vehicle related injuries'). More broadly, two thirds of diagnoses (67.8%) were coded as acute

conditions, 10.3% represented a chronic pain related condition (non-cancer), 2.6% were cancer related, 1.5% were for a mental health condition, and 10.3% indicated the presence of another non-pain related medical condition (e.g., metabolic disorders).

Medication Characteristics and Prescribing Trends over Time

From 2005 to 2016, overall frequency of opioid prescriptions increased by 86.64% (from 2470 to 4620) with the largest increase (206.15%) observed from 2005 to 2008 (2470 to 7562; see **Figure 1** and **Table 2**). Prescribing rates trended downward from 2008 to 2016, decreasing by 39.04%.

Number of patients receiving opioids per year increased by 95.10% across the study time frame (from 1736 patients in 2005 to 3387 patients in 2016; **Figure 1** or **Table 2**), with the largest increase (198.16%) occurring from 2005 to 2008, followed by a steady decrease in overall sample size through 2016 (-34.56%), mimicking trends in overall prescription frequency.

The raw number of patients receiving *multiple* prescriptions within a year increased from 391 in 2005 to 689 in 2016, but proportionally only increased from 22.53% of the total sample in 2005 to a peak of 24.96% in 2008, followed by a decrease to 20.34% in 2016 (see **Table 2**). Thus, the highest number of patients received multiple prescriptions in 2008 (n=1292) and 2009 (n=1277).

Opioid type. Regarding drug type, Oxycodone was consistently the most commonly prescribed opioid (e.g., OxyContin, Percocet; see **Table 4**). Overall rates of Oxycodone prescribing increased by 135.32% from 2005 (n=1192) to 2016 (n=2805), peaking in 2010 (n=3389). Tramadol prescriptions increased the most, marked by a 487.5% increase across study time points (from n=16 to 94), including a 600% increase from 2005 to 2013 (from n=16 to 112). Prescription rates for Fentanyl also decreased by

50.0% across the study time points, but only after increasing by 140% from 2005 (n=10) to 2012 (n=24).

Non-opioid medications. In 2016, almost twice as many individuals receiving their first opioid prescription also had an active prescription for a Benzodiazepine compared to 2005 (n=81 in 2005 and n=159 in 2016; 96.30% increase). Rates of other non-opioid medications remained stable over time.

Receipt of Single versus Multiple Prescriptions

Relative risk of receiving multiple versus single opioid prescriptions significantly increased with age and when morphine or fentanyl was the first opioid prescription type (see **Table 3**). In particular, adolescents were 1.66 times more likely to receive multiple opioid prescriptions than children age 0-5 years (95% CI= 1.58-1.52). White, English-speaking, not Hispanic/ Latino patients were also more likely to receive multiple opioid prescriptions.

Opioid-related Adverse Outcomes

A summary of the frequency of adverse events is in **Table 6** and illustrated in **Figure 2.** Broadly, large increases were observed in the frequency of adverse events from 2005 to 2016: 2200% increases in incidents of mortality, 1400% increases in patients receiving medication-assisted treatment, and 1433% increases in overdose incidents. Over half of patients with documented adverse outcomes received multiple opioid prescriptions (51.76% of patients who experienced an overdose, 59.73% of patients receiving MAT, and 57.71% of patients who died), which is a higher percentage of patients receiving multiple opioid prescriptions than observed in the total sample (31.20%).

Overdose. A total of 189 overdose incidents were reported for 170 individuals (see **Tables 6 and 7**), as indicated by overdose diagnoses, inpatient admission for treatment of overdose related symptoms, and/or administration of Naloxone. Proportionally, 0.45% of the entire sample experienced an overdose during 2005 to 2016, with the largest annual proportion of patients impacted in 2016 (1.36%) following a 119.05% increase in overdose incidents from 2015 (n=21) to 2016 (n=46). A total of 149 patients (87.60%; see **Table 7**) experienced 1 overdose, while 21 had two or more documented overdoses (12.49%). The majority of overdose incidents (98.40%; n=186) had documented involvement of an opioid (including both prescription opioids and heroin) in the encounter diagnoses, while 26.50% (n=50) had documentation of prescription opioids specifically. A total of 32 overdose incidents (16.93%) included documentation of active suicidal ideation or suicidal attempt via intentional overdose; SI was most commonly documented in overdose incidents occurring in 2006 (n=10).

Medication-Assisted Treatment (MAT). The percentage of the entire sample who received a medication for the treatment of opioid dependence (e.g., buprenorphine, naltrexone, methadone, and buprenorphine-naloxone [Suboxone]) within 1 year of receipt of an opioid prescription increased from .06% in 2006 (n=1 out of 1736) to .44% in 2016 (*n*=15 out of 3387), although was highest in 2014 (.58%; *n*=23 out of 3983).

Mortality. Data was extracted on all incidents of mortality for subjects in the study sample, not deaths only related to opioid use. Documented incidence of mortality in individuals prescribed an opioid increased from 2 individuals in 2005 to 46 in 2016 (from .12% of the sample to 1.39%), impacting a total of 201 patients. Similar to overdose incident rates, mortality incidents increased most significantly from 2015 (n=23) to 2016 (n=46; an increase of 100%). Cause of mortality was unknown for most patients. On

average, deaths occurred 3.40 years (*sd*= 3.24; range 0-13 years) after receipt of the first opioid prescription.

Differences in Outcomes Based on Medication and Individual Characteristics

Table 8 includes a summary of medication-related and demographic characteristics of patients with documented markers of morbidity and mortality following receipt of an opioid prescription as well as relative risk of experiencing adverse outcomes based on these characteristics. Overall, increased risk for adverse outcomes differed significantly based on type of first opioid prescription, older age, minority status (specifically for mortality), encounter type, payer status, and receipt of multiple prescriptions.

Medication characteristics.

Year of first opioid. Patients who died or received MAT most commonly received their first opioid prescription in 2012 or earlier. Patients who experienced an overdose most commonly received their first opioid prescription from 2006- 2009, consistent with overall prescribing trends.

Type of first opioid prescription. Patients who experienced an overdose or received MAT were most commonly prescribed Oxycodone. Receipt of Morphine was associated with a 22.40-fold (95 CI=13.5-37.15**)** increased risk of receiving MAT and a 64.39-fold increased risk of death (95% CI= 44.91-92.34) than Oxycodone. Similarly, the risk of receiving MAT or of mortality after receipt of a Tramadol prescription was 3.32 times (95% CI= 1.23-8.96) and 32.63 times (95% CI= 8.75-121.69) greater than Oxycodone.

Encounter type. Patients receiving MAT and patients who died most commonly received their first opioid prescription during discharge from an inpatient admission

(39.60%, n=59; 42.20%, n=85, respectively). In relation to the total sample, 1.20% of the sample (n=65) who received an opioid prescription during an outpatient encounter died. Subsequently, relative risk for adverse outcomes was significantly reduced when receiving the first opioid prescription during an emergency, inpatient discharge, or day surgery encounter in comparison to outpatient encounters.

Frequency of opioid prescription. A larger proportion of patients receiving multiple opioid prescriptions experienced adverse outcomes as compared to patients who received only one opioid prescription. Most notably, of all patients who received 4 or more opioid prescriptions, 1.20% experienced an overdose (n=35), 1.48% received MAT (n=43), and 2.16% died (n=63). For comparison, 0.21-0.29% of all patients who received a single opioid prescription experienced an adverse outcome. Relative risk of adverse outcomes for individuals receiving multiple opioid prescriptions versus single prescriptions steadily increased as number of prescriptions increased. In particular, in patients who received 4 or more opioid prescriptions, the risk of overdose was 4.23 times greater (95% CI= 2.86-6.28), the risk of receiving MAT was 7.11 times greater (95% CI= 4.81-10.50), and the risk of mortality was 7.35 times greater (95% CI=5.32-10.16).

Individual characteristics.

Age at first opioid prescription. The majority of patients who experienced an overdose (94.12%, n=160) or received MAT (87.24%, n=130) received their first opioid prescription during adolescence (age 12-17 years) or as a young adult (age 18-21 years). Subsequently, adolescents and young adults were at increased risk of adverse events relative to youth age 11 and under, particularly overdose (RR=8.18, 95% CI= 4.32-15.49) and MAT (RR=3.50, 95% CI= 2.16-5.66). Age at first opioid prescription in patients who died was more varied: 32.34% (n=65) of deceased patients received their first opioid

prescription during adolescence, while 28.86% were age 0-5 years are receipt of first opioid (n=58).

Sex. Males were 1.35 times more likely to die (95% CI- 1.01-1.79) in comparison to females. Proportionally, more females than males received MAT (58.39%, n=87).

Ethnicity, Race, and Primary Language. Proportionally, within the entire sample, more racial minority patients died than white patients. Specifically, 4.34% (n=18) of all Asian patients, 2.17% of all Black/ Africa American patients, and 1.45% of American Indian/ Alaska Native patients died in comparison to 0.43% of all White patients; however, frequency of death was highest among White patients (42.29%, n=85) followed by American Indian/ Alaskan Native patients (32.84%, n=66). Additionally, relative risk of death was significantly greater in minority patients in comparison to White patients (3.41-10.20x greater). Equal proportions of the entire sample of Hispanic/Latino and Not Hispanic/Latino identifying patients died (.45% and .46%, respectively), although a greater frequency of deaths occurred in Hispanic/Latino patients (n=96, 46.27%, vs. n=53, 26.37%, of Non-Hispanic/Latino patients).

Overdose occurred most often in Hispanic/Latino (n=95, 55.89%, 0.45% of the total sample) and White patients (n=101, 59.42% of overdoses; 0.51% of the total sample. Similarly, Hispanic/Latino patients (n=90, 60.40%, 0.43% of the total sample) and White patients (n=91, 61.07%, 0.46% of the total sample) were more likely to receive MAT. Proportionally, within the entire sample, a marked 6.27% (n=26) of Asian patients received MAT and these patients were at 13.27 times higher risk (95% CI= 9.00-21.04) of receiving MAT compared to White patients. Primary language was English for nearly all patients experiencing adverse outcomes (87.56%- 96.79%), consistent with the full sample.

Payer Status. Public/government assistance (e.g., Medicaid) was the most common type of insurance for patients experiencing all three outcomes (42.78%-60.70%). Patients who were uninsured were 2.93 times more likely to experience an overdose (95% CI= 1.96-4.39) and 2.42 more likely to receive MAT (95% CI= 1.47-4.01) when compared to privately insured patients.

Chapter 4

Discussion

The current study utilized pre-existing data drawn from the medical records system of a large university hospital to evaluate opioid prescription rates to youth in New Mexico (NM), as rates of prescription of opioids to children and adolescents at a statewide level were unknown. Further, individual factors and outcomes associated with receipt of single or repeat prescriptions and adverse outcomes were characterized to increase understanding of the prevalence and impact of opioid prescriptions. This large and comprehensive dataset captured several important variables, which allowed for examination of relations amongst hypothesized risk factors and opioid-related outcomes following the last opioid prescription. **Unique aspects of this study are the racial and ethnic diversity of the sample, geographic location (rural, high-risk state for opioid use), utilization of hospital medical records data (rather than insurance claims data or data gathered via patient self-report), consideration of individual factors associated with receipt of multiple opioid prescriptions, and preliminary evaluation of longitudinal outcomes following receipt of an opioid prescription.**

Overall, substantial increases in prescription of opioids to youth in New Mexico as well as rates of opioid-related morbidity and mortality were observed. Despite downward trends in prescribing rates from 2008 to 2016, increases in opioid-related morbidity and mortality persisted. Patients who were older, White, not Hispanic/ Latino, and English-speaking were more likely to receive multiple opioid prescriptions, which is consistent with previous literature related to individual factors associated with receipt of any opioid (Groenewald et al., 2015; Pletcher et al., 2008; Sadhasivam et al., 2012; Wu et al., 2011), but not necessarily multiple opioids, as we are not aware of any preexisting

data in that domain. Increased risk of adverse outcomes was observed in patients receiving more than one opioid prescription, as well as patients who were older, of a minority racial background, publicly insured or uninsured, and who received Tramadol, Fentanyl, or Morphine as a first opioid prescription. Limitations of the current dataset did not allow for examination of some previously identified risk factors for opioid misuse in youth, including the presence of chronic pain, exposure to trauma, and other substance use (Groenewald, Law, Fisher, Beals-Erickson, & Palermo, 2019). A unique finding in this sample is that Asian patients, who comprised a small subset of the sample (1.0%) and represent a small subset of the overall population in New Mexico, had significantly proportionally higher rates of adverse events including much higher risk for receiving medication-assisted treatment (MAT) and death.

Results from the present study suggest that prescription of opioids to youth in New Mexico is occurring with greater frequency in comparison to national prescribing trends, such as those reported by Groenewald et al. (2015). Interestingly, Groenewald et al. (2015) found that overall prescribing rates to youth in the United States remained stable and low, but significant increases in youth receiving 5 or more opioid prescriptions were observed. In contrast, rates of youth receiving multiple opioids in this dataset did not increase substantially over time. Thus, prescribing trends to youth in New Mexico appear more similar to adult prescribing trends in the US (Manchikanti et al., 2010; Shaheed et al., 2016; Vowles et al., 2015), particularly when examined in relation to the high rates of opioid-related morbidity and mortality. In line with national findings in adults, decreases in opioid prescribing within this sample did not equate to decreases in opioid-related morbidity and mortality (Centers for Disease Control and Prevention

National Center for Health Statistics, 2015; Jones et al., 2013; Rudd et al., 2016; Vowles et al., 2015).

Although not explicitly captured in this dataset, there are several identified "risk factors" (Groenewald et al., 2019) for opioid misuse that are common among youth in New Mexico that likely make them more vulnerable to adverse outcomes and may explain differences in state versus national rates. Specifically, New Mexico consistently ranks as among the worst states for high rates of childhood trauma (a risk factor which has been linked to opioid use in adulthood (Groenewald et al., 2019)), including substance use in utero and high rates of infants born drug-dependent, as well as adolescent substance use (Gallagher et al., 2018). Geographically New Mexico is primarily rural and demographically, ethnically diverse. Previous work has identified adolescents living in rural areas as being at 35% greater odds of engaging in prescription opioid misuse (Monnat & Rigg, 2015) and high opioid prescribing rates have been recorded geographically in the southern United States (Rolheiser, Cordes, & Subramanian, 2018), but not NM in particular. Additionally, unmanaged pain has been repeatedly identified as a primary motive for nonmedical opioid use in adolescents (e.g. McCabe, West, & Boyd, 2013b). One potential driver of opioid prescribing and misuse rates in a rural state such as New Mexico could be difficulty accessing non-pharmacological evidence-based pain management resources, due to geographic location and/or lack of availability of these resources. At this time, New Mexico does not have a specialized interdisciplinary pediatric pain rehabilitation program (American Pain Society, 2015), the gold standard of treatment for disabling chronic pain (Hechler et al., 2015). Additionally, given that over a third of youth in New Mexico grow up in poverty,

several barriers may be present to traveling out of state for specialized treatment (Gallagher et al., 2018).

While cause of death for patients in the sample is unknown, the large increase in mortality within the sample is perplexing and worrisome. Death rates in children and adolescents within the state have not increased, although, drug overdose deaths in New Mexico have risen since 2001 (Gallagher et al., 2018). Consistent with the present sample, American Indian youth in New Mexico die at more than twice the rate of other racial groups. Nationally, rates of adolescents dying from opioid-related complications are increasing, with a notable increase from 2014-2015 (Curtain et al., 2017). A notable subset of early childhood aged children died (age 0-5 years; n=58, .78% of the total sample of that age group). Since cause of death was unknown, it is hard to know if this may be related to accidental injury/ overdose of opioids or perhaps greater disease severity (e.g. cancer). Similarly, Fentanyl use with children is fairly rare, except during palliative care; thus it is recommended that the finding that youth prescribed Fentanyl were more likely to die should be interpreted with caution and within this clinical context, rather than in relation to rising Fentanyl-related death rates in the US.

Increases in youth receiving medication-assisted treatment (MAT) for an opioid use disorder is a finding that comes with mixed implications. It is hard to know if this is reflective of an increase in incidence of opioid use disorders (OUD) or an increase in patients accessing treatment for an OUD; it is also unclear if MAT is being administered for prescription opioid dependency or heroin dependency. Increases in adolescents and young adults seeking MAT for an opioid use disorder further highlights previous findings (Greenfield et al., 2014) regarding the need to increase access to developmentally appropriate behavioral based treatments in conjunction with MAT in New Mexico. It is

well documented that patient abstinence and adherence rates while receiving MAT remain sub-optimal (Krupitsky et al., 2011; Ling et al., 2010; Mattick, Breen, Kimber, & Davoli, 2009; Resnick et al., 1992). For adolescents and young adults, in particular, developmentally appropriate behavioral treatments combined with MAT are recommended (COMMITTEE ON SUBSTANCE USE AND PREVENTION, 2016).

Finally, results in the current study underscore previously documented relations between non-medical prescription opioid use and suicidal ideation (Divin & Zullig, 2014), suggesting a need for interventions that address co-morbid mental health needs in concert with pain treatment. This finding also underscores the importance of safe storage and disposal of leftover opioids, as increased access to means for suicide increases risk of attempt and completion. Future research should carefully monitor suicidal ideation in youth prescribed an opioid to determine if the patient is at significant risk for intentional overdose. Relatedly, this work highlights the need for careful screening of identified factors associated with increased risk of adverse outcomes and risky use to inform opioid prescribing and prescription monitoring practices (e.g. CRAFFT [Knight, Sherritt, Shrier, Harris, & Chang, 2002; McCabe et al., 2012]). Additional measure development is needed in this area, however, to ensure that measures are valid and reliable in diverse populations and do not inappropriately restrict patients from adequate pain management.

Limitations

A feasible way to understand the evolution of opioid prescribing to youth and identify relevant individual characteristics is to examine existing data. A limitation of this approach is that data were not collected prospectively, nor was the database designed specifically to accomplish the study aims. Instead these data come from a clinical database which did not capture all variables of interest. The “real world” nature of these

data means that they still contain many relevant variables, and the retrospective aspect lends itself to immediate availability, perhaps offsetting this limitation. Further, the hospital data archives can only extract data from 2005 onwards, when the electronic medical record was implemented, naturally limiting the study timeframe. Thus, study aims could not be evaluated prior to that date. There is also no way to confirm whether or not opioid prescriptions were filled, if patients sought additional prescriptions from providers outside of the university hospital system, or if the first opioid prescription received during the study timeframe was truly the patient's first exposure to being prescribed an opioid (e.g. patients may have received an opioid prescription before 2005). Frequency of adverse outcomes are also limited to those treated within the UNMH hospital system. Further, adverse events cannot be causally linked to receipt of an opioid prescription, however it is known that they occurred temporally after receipt of an opioid prescription. This dataset also likely only captures a subset of American Indian/ Alaska Native youth in New Mexico, as many AI/AN families in New Mexico receive care through Indian Health Services. Additionally, due to deidentification procedures, prescriptions dates could only be provided in years, rather than month and year and prescription start/ stop dates were not available; thus it was not possible to accurately calculate length of time between prescriptions. Finally, while it was intended to calculate Morphine Equivalent Dose (MED) to look at changes in dosing over time and associations with different baseline characteristics (e.g. race/ ethnicity), less than 20% of prescriptions had adequate data (e.g. dose and frequency) to calculate MED. Thus, we were unable to perform those analyses. It is also a limitation that a subset of patients declined to report or had missing values for race (27.1%) and/or ethnicity (22.5%).

Conclusions and Significance

As life expectancy in the United States has declined for two years in a row, attributable largely to the increase in opioid overdose mortality among young adults and adults (Kochanek et al., 2017), the importance of quantifying opioid prescription rates to youth, a key access point for nonmedical use, and associated adverse outcomes cannot be overstated. This is the first epidemiological study using hospital level data to examine opioid prescribing rates and associated longitudinal outcomes to children and adolescents in a high-risk state. Much of the available research on opioid prescribing rates to youth has been primarily derived from insurance claim databases (e.g. Groenewald et al., 2015; Richardson et al., 2011), rather than medical records data, limiting the clinical utility and generalizability of findings. Contributions from this research address several gaps in our understanding of opioid prescribing trends to children and adolescents including: 1) comprehensive quantitative measurement of prescribing rates of opioids to youth in New Mexico, 2) identification of individual factors in multiple domains associated with receipt of multiple opioid prescriptions and adverse outcomes 3) examination of prevalence of longitudinal outcomes (e.g. morbidity and mortality) after receipt of an opioid prescription.

In particular, this study contributes to the growing literature base identifying factors associated with receipt of opioid prescriptions in youth and risk factors predictive of less favorable outcomes, including overdose and death. A new finding from this dataset is that, consistent with adult literature, receipt of more than one opioid prescription was associated with greater risk for opioid-related adverse consequences, highlighting potential additive risks of adverse outcomes when pediatric patients receive single versus multiple opioid prescriptions. This finding needs to be replicated in other samples of youth. Finally, the large difference in trends of opioid prescribing rates to

youth in New Mexico versus nationally indicates that national statistics may not be accurately representative of all states. In order to effectively and appropriately distribute intervention and treatment resources to the highest need areas, trends may need to be evaluated locally.

Figure 1.
Opioid prescribing trends over time in individuals who received single or multiple opioid prescriptions

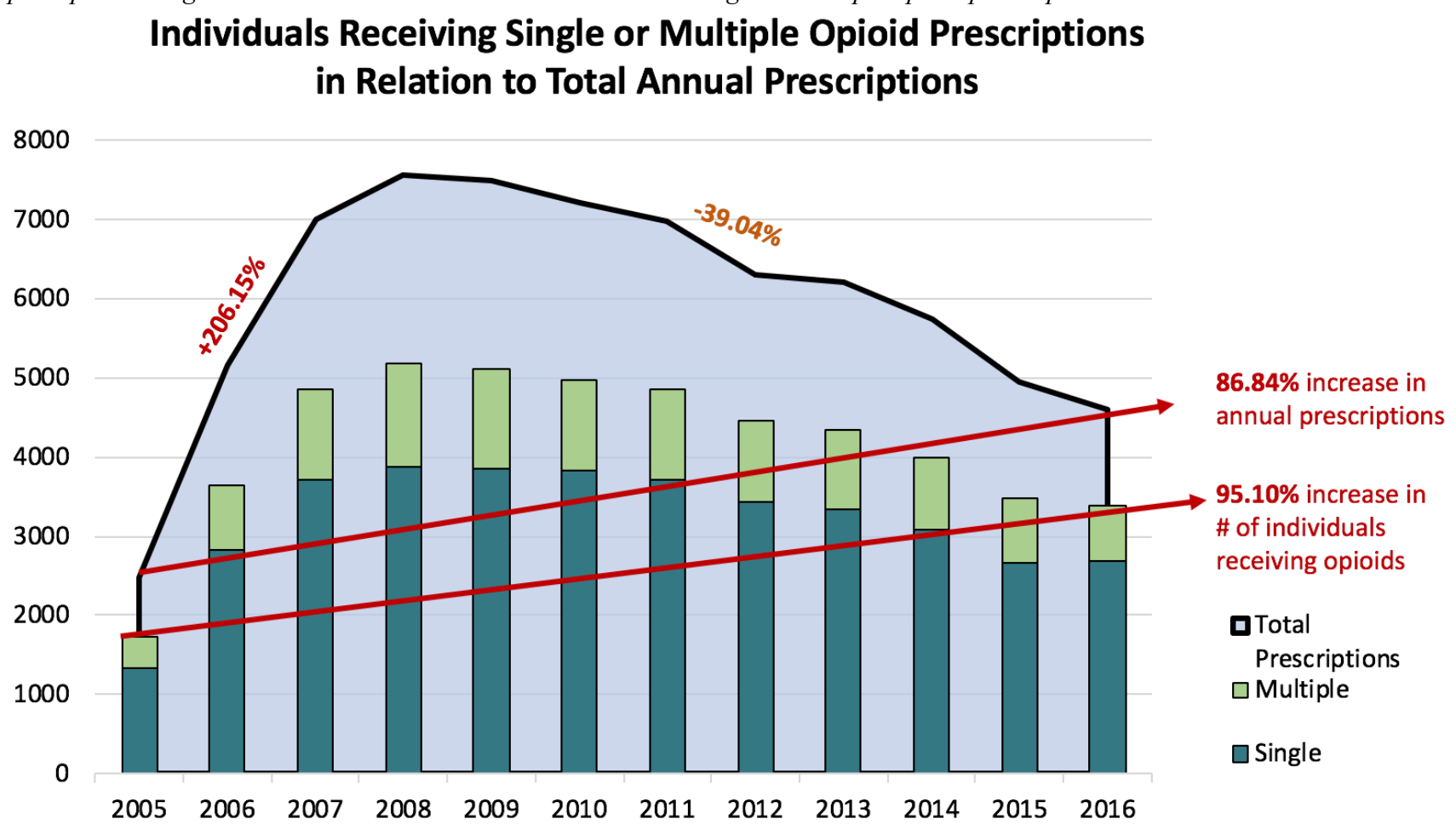

Figure 2.
Trends in adverse events in patients who received at least one opioid prescription

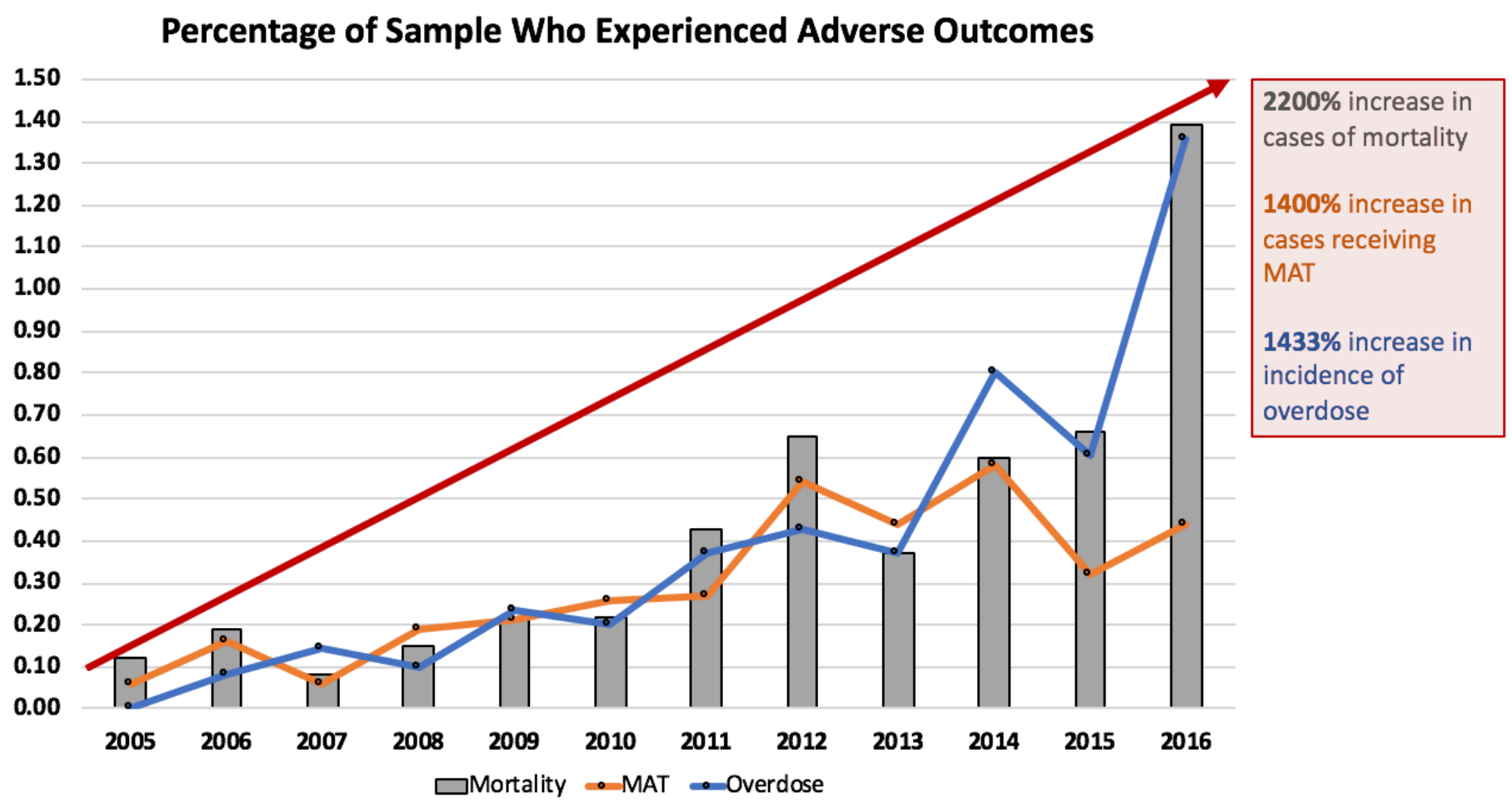

Table 1.
Variables extracted from patient electronic medical records

Inclusion criteria: Age 0-21, Prescribed an opioid during an outpatient encounter (e.g. Emergency Department, discharge from an inpatient admission, day surgery, or outpatient clinic)
Exclusion criteria: Inpatient opioid prescription encounters

Variables of interest

Individual/ baseline *Data extracted once for each patient*	**Opioid prescription encounter** *Data extracted from each encounter where an opioid was prescribed*	**Adverse outcomes** *Data extracted from each clinical encounter for 12 months following first or last prescription*
Age	*Medication-related characteristics:*	*Markers of morbidity*
Sex	Encounter location	Overdose (admission, ED encounter)
Ethnicity	Name of drug	Medication-Assisted Treatment
Race	Prescribed dose	Death
Primary language	Duration/ dispense value	*Subsequent diagnoses*
Payer status	Total # of opioid prescriptions	
Non-opioid prescriptions	Number of years receiving	
Other pain medications	multiple opioid prescriptions	
Psychiatric medications	*Active diagnoses*	
Premorbid diagnoses		

Note. An "encounter" is defined as a unique clinical instance of direct provider to patient interaction; *Payer status*= Public/ Government Assistance (e.g. Medicaid), Private, or Uninsured; *Encounter location*= Emergency, discharge from inpatient, outpatient, or day surgery; *Diagnoses* will also coded as Acute, Chronic pain, Mental Health, Other Co-Morbid Condition, or Cancer Related; *Prescribed dose* will be converted to Morphine Equivalent Dose.

Table 2.
Annual sample characteristics including total opioid prescriptions and frequency of individuals receiving single vs. multiple prescriptions

Year	Total annual opioid prescriptions	Total patients receiving their first opioid prescription*	Total patients who received an opioid prescription**	Patients who received a single opioid prescription	Patients who received multiple opioid prescriptions	% of sample receiving multiple opioid prescriptions
2005	2470	1733	1736	1345	391	22.52%
2006	5150	3431	3644	2830	814	22.34%
2007	7000	4374	4864	3725	1139	23.42%
2008	7562	4439	5176	3884	1292	24.96%
2009	7487	4280	5124	3847	1277	24.92%
2010	7215	4128	4980	3839	1141	22.91%
2011	6974	3940	4846	3704	1142	23.57%
2012	6295	3574	4452	3443	1009	22.66%
2013	6203	3503	4337	3343	994	22.92%
2014	5736	3153	3983	3081	902	22.65%
2015	4945	2777	3470	2658	812	23.40%
2016	4610	2688	3387	2698	689	20.34%
TOTAL	**71647**	**42020**	**49999**	**38397**	**11602**	**23.20%**

*Represents number of unique patient in the dataset.
**This includes more patients than in the first column because some individuals received prescriptions in multiple years. Thus, each patient is counted only once per year, but may show up in multiple years.

Table 3.
Medication-related and demographic characteristics at receipt of first opioid of patients who received single vs. multiple prescriptions

	Full Sample *N*= 42,020		**Single opioid *N*=28,911**		**Multiple opioid *N*= 13,109**		**Relative risk for multiple opioids**
	N	**%**	***N***	**%**	***N***	**%**	**(95% CI)**
Year of first prescription							
2005†	1,733	4.1%	1047	3.6%	686	5.2%	REF
2006	3,431	8.2%	2182	7.5%	1249	9.5%	**.92 (.85-.99)**
2007	4,374	10.4%	2827	9.8%	1547	11.8%	**.89 (.83-.96)**
2008	4,439	10.6%	2858	9.9%	1581	12.1%	**.90 (.84-.97)**
2009	4,280	10.2%	2807	9.7%	1473	11.2%	**.87 (.81-.93)**
2010	4,128	9.8%	2827	9.8%	1301	9.9%	**.80 (.74-.86)**
2011	3,940	9.4%	2754	9.5%	1186	9.0%	**.76 (.71-.82)**
2012	3,574	8.5%	2543	8.8%	1031	7.9%	**.73 (.67-.79)**
2013	3,503	8.3%	2522	8.7%	981	7.5%	**.71 (.65-.77)**
2014	3,153	7.5%	2315	8.0%	838	6.4%	**.67 (.62-.73)**
2015	2,777	6.6%	2044	7.1%	733	5.6%	**.67 (.61-.73)**
2016	2,688	6.5%	2185	7.6%	503	3.8%	**.47 (.43-.52)**
Total opioid prescriptions							
1	28,911	68.8%	28,911	100%	--	--	--
2	7,460	17.8%	--	--	7,460	56.9%	--
3	2,734	6.5%	--	--	2,734	20.9%	--
4 or more	2,915	6.9%	--	--	2,915	22.2%	--
First opioid prescription type							
Oxycodone†	19,318	46.0%	12547	43.4%	6771	51.6%	REF
Hydrocodone	15,331	36.5%	11120	38.5%	4211	32.1%	**.78 (.76-.81)**
Codeine	6,907	16.4%	5006	17.3%	1901	14.5%	**.79 (.75-.82)**
Tramadol	253	0.6%	154	0.5%	99	0.8%	1.12 (.96-1.30)
Morphine	150	0.4%	57	0.2%	93	0.7%	**1.77 (1.56-2.01)**
Fentanyl	16	<.1%	6	0.02%	10	0.01%	**1.78 (1.22-2.61)**
Other	45	.1%	21	0.1%	24	0.2%	**1.52 (1.16-2.00)**

	Full Sample *N*= 42,020		Single opioid *N*=28,911		Multiple opioid *N*= 13,109		Relative risk for multiple opioids
	N	%	*N*	%	*N*	%	(95% CI)
Age							
Early childhood (0-5 years) †	7,432	17.7%	5780	20.0%	1652	12.6%	REF
School age (6-11 years)	6,790	16.2%	4829	16.7%	1961	15.0%	**1.30 (1.23-1.37)**
Adolescent (12-17 years)	11,471	27.3%	7240	25.0%	4231	32.3%	**1.66 (1.58-1.52)**
Young-adult (18-21 years)	16,327	38.9%	11,062	38.3%	5265	40.2%	**1.45 (1.38-1.52)**
Sex							
Female †	18,927	45.0%	12,974	44.9%	5,953	45.4%	REF
Male	23,093	55.0%	15,937	55.1%	7,156	54.6%	.99 (.96-1.01)
Ethnicity							
Not Hispanic/ Latino†	11,496	27.4%	7618	26.3%	3878	29.6%	REF
Hispanic/ Latino	21,044	50.1%	14364	49.7%	6681	51.0%	**.94 (.91-.97)**
Not reported	9,480	22.5%	6929	24.0%	2550	19.5%	--
Race							
White†	19,985	48.3%	13,239	46.5%	6746	52.2%	REF
American Indian/Alaska Native	4553	11.0%	3144	11.0%	1409	10.9%	**.92 (.87-.96)**
Black/African American	1292	3.1%	835	2.9%	457	3.5%	1.05 (.97-1.13)
Two or More Races	539	1.3%	372	1.3%	167	1.3%	.92 (.81-1.04)
Asian	415	1.0%	313	1.1%	102	0.8%	**.73 (.61-.86)**
Hawaiian Native/ Pacific Islander	96	0.2%	65	0.2%	31	0.2%	.96 (.72-1.28)
Other	3295	8.0%	2579	9.1%	716	5.5%	--
Decline to answer/ unavailable	11,241	27.1%	7946	27.9%	3295	25.5%	--
Primary language							
English†	37,243	88.9%	25,455	88.3%	11,788	90.2%	REF
Spanish	3,755	8.9%	2776	9.6%	979	7.5%	**.82 (.78-.87)**
Other/ Not reported	894	2.1%	588	2.0%	306	2.3%	--
Encounter type							
Outpatient†	5,401	12.9%	3272	11.3%	2129	16.3%	REF
Emergency	14,954	35.6%	11,017	38.1%	3937	30.0%	**.67 (.64-.70)**
Discharge from inpatient	12,364	29.4%	7682	26.6%	4682	35.7%	**.96 (.92-1.00)**

	Full Sample *N*= 42,020		Single opioid *N*=28,911		Multiple opioid *N*= 13,109		Relative risk for multiple opioids
	N	**%**	***N***	**%**	***N***	**%**	**(95% CI)**
Day surgery	9,301	22.1%	6940	24.0%	2361	18.0%	**.64 (.61-.68)**
Payer status							
Private/ Commercial†	14,116	33.6%	9619	33.2%	4497	34.2%	REF
Public/ Government assistance	21,027	50.1%	14,304	49.5%	6723	51.3%	1.00 (.97-1.04)
Uninsured	6863	16.3%	4981	17.2%	1882	14.4%	**.86(.82-.90)**
Non-opioid drugs							
Benzodiazepines	1,465	3.5%	718	2.48%	747	5.70%	--
Muscle Relaxant	618	1.5%	394	1.36%	224	1.71%	--
SSRI/ SNRI	163	0.4%	74	0.26%	89	0.68%	--
Anticonvulsants	19	<.1%	10	0.03%	9	0.07%	--
Tricyclic anti-depressants	18	<.1%	7	0.02%	11	0.08%	--
Barbiturates	8	<.1%	5	0.02%	3	0.02%	--

† Patients with this characteristic served as the reference group; CI denotes confidence interval; Bold values indicate statistically significant values based on the CI. RR for receiving multiple opioids in patients who also received non-opioid drugs was not calculated, as there is not a hypothesis driven rationale for identifying a reference group.

Table 4.
ICD-9 chapters for presenting diagnoses at encounter for first opioid prescription (baseline)

ICD-9 Chapter	***N***
Injury And Poisoning	34,416
Supplementary Classification Of External Causes Of Injury And Poisoning	18,142
Supplementary Classification Of Factors Influencing Health Status And Contact With Health Services	12,152
Symptoms, Signs, And Ill-Defined Conditions	10,998
Diseases Of The Musculoskeletal System And Connective Tissue	10,224
Diseases Of The Respiratory System	8333
Diseases Of The Nervous System And Sense Organs	8205
Diseases Of The Genitourinary System	4690
Diseases Of The Digestive System	4320
Complications Of Pregnancy, Childbirth, And The Puerperium	4012
Congenital Anomalies	3662
Diseases Of The Skin And Subcutaneous Tissue	1966
Mental Disorders	1899
Neoplasms	1869
Diseases Of The Circulatory System	1713
Diseases Of The Blood And Blood-Forming Organs	1360
Endocrine, Nutritional And Metabolic Diseases, And Immunity Disorders	1252
Infectious And Parasitic Diseases	484
Certain Conditions Originating In The Perinatal Period	88

Table 5.
Frequency of opioid prescribing over time by type of opioid

Opioid type	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**TOTAL**
Oxycodone	1192	2176	2876	3417	3609	3839	3453	3287	3162	3065	2958	2805	35839
Hydrocodone	675	1859	2425	2316	2238	1958	2637	2379	2393	2192	1744	1530	24346
Codeine	536	999	1589	1672	1441	1149	611	425	367	218	77	81	9165
Morphine	28	60	33	42	102	146	125	64	95	106	43	75	919
Tramadol	16	17	43	66	53	67	71	75	112	108	96	94	818
Other	13	16	19	30	26	41	56	41	54	42	26	20	384
Fentanyl	10	23	15	19	18	15	21	24	20	5	1	5	176
Yearly Total	2470	5150	7000	7562	7487	7215	6974	6295	6203	5736	4945	4610	71647

Table 6.
Frequency of markers of morbidity and mortality by year in patients who received single vs. multiple opioid prescriptions

Year	Total patients who received an opioid prescription	Overdose Incidents				Patients Receiving Medication-Assisted Treatment (MAT)				Mortality Incidents			
		Single*	Multiple*	Total	% of *annual* sample*	Single*	Multiple*	Total	% of *annual* sample*	Single*	Multiple*	Total	% of *annual* sample*
2005	1736	0	0	0	0%	0	1	1	0.06%	2	0	2	0.12%
2006	3644	3	0	3	0.08%	2	4	6	0.16%	2	5	7	0.19%
2007	4864	4	3	7	0.14%	0	3	3	0.06%	2	2	4	0.08%
2008	5176	2	3	5	0.10%	3	7	10	0.19%	5	3	8	0.15%
2009	5124	4	8	12	0.23%	3	8	11	0.21%	5	6	11	0.21%
2010	4980	7	3	10	0.20%	6	7	13	0.26%	3	8	11	0.22%
2011	4846	6	12	18	0.37%	5	8	13	0.27%	8	13	21	0.43%
2012	4452	7	12	19	0.43%	13	11	24	0.54%	10	19	29	0.65%
2013	4337	6	10	16	0.37%	10	9	19	0.44%	9	7	16	0.37%
2014	3983	16	16	32	0.80%	12	11	23	0.58%	9	14	23	0.60%
2015	3470	11	10	21	0.61%	4	7	11	0.32%	6	17	23	0.66%
2016	3387	26	20	46	1.36%	2	13	15	0.44%	24	22	46	1.39%
TOTAL	---	92	97	189	0.45%**	60	89	149	0.35%**	85	116	201	0.48%**

*Denotes if the incident occurred in a patient who received single or multiple opioid prescriptions during the study timeframe.
**Percentage of total sample was calculated out of 42,020, number of unique patients in the dataset.

Table 7.
Characteristics associated with overdose incidents.

Year	Unique patients who experienced an overdose by year N=170*	Total overdose incidents	Documentation of active suicidal ideation or attempt via intentional overdose
2005	0	0	1
2006	3	3	10
2007	7	7	1
2008	5	5	3
2009	11	12	4
2010	9	10	2
2011	17	18	4
2012	19	19	1
2013	14	16	1
2014	29	32	1
2015	19	21	2
2016	37	46	2
TOTAL	*	189	32 (16.93% of incidents)

Documented substances at overdose	**%**	***N***
Unspecified opioid	41.30%	78
Heroin	30.70%	58
Prescription opioids	22.80%	43
Prescription opioids & heroin	3.70%	7
Other substance	1.60%	3

Total Number of Overdoses	**%**	***N***
1	87.60%	149
2	9.40%%	16
3	1.80%%	3
4	1.20%%	2

*Number of unique patients who experienced an overdose =170; since some patients experienced more than one overdose, they are counted in multiple years.

Table 8.
Medication and demographic characteristics of patients with markers of morbidity and mortality after an opioid prescription

	Overdose *N*= 170		**Medication-Assisted Treatment (MAT) *N*= 149**		**Mortality *N*= 201**	
	***N* (% total sample)**	**Relative Risk (95% CI)**	***N* (% total sample)**	**Relative Risk (95% CI)**	***N* (% total sample)**	**Relative Risk (95% CI)**
Year of first opioid						
2005†	8 (.46%)	REF	6 (.35%)	REF	13 (.75%)	REF
2006	29 (.85%)	1.83 (.84-4.00)	8 (.23%)	0.67 (.23-1.94)	26 (.76%)	1.01 (.52- 1.96)
2007	21 (.48%)	1.04 (.46-2.34)	11 (.25%)	0.73 (.27-1.96)	26 (.59%)	0.79 (.41-1.54)
2008	21 (.47%)	1.02 (.45-2.31)	9 (.20%)	0.59 (.21-1.64)	22 (.50%)	0.66 (.33-1.31)
2009	23 (.54%)	1.16 (.52-2.60)	21 (.49%)	1.42 (.57-3.51)	15 (.35%)	0.47 (.22-.98)
2010	22 (.53%)	1.15 (.51-2.69)	19 (.46%)	1.33 (.53-3.32)	22 (.53%)	0.71 (.36-1.41)
2011	12 (.30%)	0.66 (.27-1.61)	9 (.23%)	0.66 (.24-1.85)	21 (.53%)	0.71 (.36-1.41)
2012	10 (.28%)	0.61 (.24-1.53)	24 (.67%)	1.94 (.79-4.74)	21 (.59%)	0.78 (.39-1.56)
2013	8 (.23%)	0.49 (.19-1.32)	15 (.43%)	1.24 (.48-3.18)	8 (.23%)	0.30 (.13-.73)
2014	10 (.32%)	0.69 (.27-1.74)	12 (.38%)	1.10 (.41-2.92)	11 (.35%)	0.47 (.21-1.04)
2015	2 (.07%)	**0.16 (.03-.73)**	9 (.32%)	0.94 (.33-2.63)	9 (.32%)	0.43 (.19-1.01)
2016	4 (.15%)	0.32 (.10-1.07)	6 (.22%)	0.64 (.21-2.00)	7 (.26%)	0.35 (.14-.87)
Total opioids						
Single†	82 (.28%)	REF	60 (.21%)	REF	85 (.29%)	REF
Multiple	88 (.67%)	**2.37(1.75-3.20)**	89 (.68%)	**3.27 (2.36-4.54)**	116	**3.01 (2.27-3.97)**
2	36 (.48%)	**1.70 (1.15-2.52)**	34 (.46%)	**2.20 (1.44-3.34)**	27 (36%)	**1.23 (.80-1.90)**
3	17 (.62%)	**2.19 (1.30-3.69)**	12 (.44%)	**2.11 (1.14-3.93)**	26 (.95%)	**3.23 (2.09-5.01)**
4 or more	35 (1.20%)	**4.23 (2.86-6.28)**	43 (1.48%)	**7.11 (4.81-10.50)**	63 (2.16%)	**7.35 (5.32-10.16)**
First opioid type						
Oxycodone†	107 (.55%)	REF	92 (.48%)	REF	74 (.36%)	REF
Hydrocodone	47 (.31%)	**.55 (.39-.78)**	24 (.16%)	**.33 (.31-.51)**	46 (.30%)	.78 (.54-1.13)
Codeine	12 (.17%)	**.31 (.17-.57)**	11 (.16%)	**.33 (.18-.62)**	40 (.58%)	1.51 (1.03-2.22)
Tramadol	3 (1.19%)	2.14 (.68-6.70)	4 (1.58%)	**3.32 (1.23-8.96)**	1 (.40%)	1.03 (.14-7.39)
Morphine	0	--	16 (10.67%)	**22.40 (13.5-37.15)**	37 (24.67%)	**64.39 (44.91-92.34)**
Fentanyl	0	--	0	--	2 (12.5%)	**32.63 (8.75-121.69)**
Age at first opioid						
0-11 years†	10 (.07%)	REF	19 (.13%)	REF	94 (.66%)	REF

	Overdose *N*= 170		Medication-Assisted Treatment (MAT) *N*= 149		Mortality *N*= 201	
	***N* (% total sample)**	**Relative Risk (95% CI)**	***N* (% total sample)**	**Relative Risk (95% CI)**	***N* (% total sample)**	**Relative Risk (95% CI)**
AYA (12-21 years)	160 (.58%)	**8.18 (4.32-15.49)**	130(.47%)	**3.50 (2.16-5.66)**	107 (.38%)	**.58 (.44-.77)**
0-5 years†	3 (.04%)	REF	12 (.16%)	REF	58 (.78%)	REF
6-11 years	7 (.10%)	2.55 (.66-9.87)	7 (.10%)	.62 (.25-1.62)	36 (.53%)	.68 (.45-1.03)
12-17 years	39 (.34%)	**8.42 (2.60-27.25)**	39 (.34%)	**2.11 (1.10-4.01)**	65 (.57%)	.73 (.51-1.03)
18-21 years	121 (.74%)	**18.36 (5.84-57.71)**	91(.56%)	**3.52 (1.88-6.26)**	42 (.26%)	**.33 (.22-.49)**
Sex						
Female†	71 (.38%)	REF	87 (.46%)	REF	76 (.40%)	REF
Male	99 (.43%)	1.14 (.84-1.55)	62 (.27%)	**.58 (.42-.15)**	125 (.54%)	**1.35 (1.01-1.79)**
Ethnicity						
Not Hispanic/ Latino†	53 (.46%)	REF	40 (.35%)	REF	53 (.46%)	REF
Hispanic/ Latino	95 (.45%)	.98 (.70-1.37)	90 (.43%)	1.23 (.85-1.78)	93 (.45%)	.97 (.70-1.36)
Not reported	24 (.25%)	--	19 (.20%)	--	55 (.19%)	--
Race						
White†	101 (.51%)	REF	91 (.46%)	REF	85 (.43%)	REF
AI/AN	19 (.42%)	.83 (.51-1.35)	17 (.37%)	.82 (.49-1.37)	66 (1.45%)	**3.41 (2.48-4.69)**
Black/AA	15 (1.16%)	**2.30 (1.34-3.94)**	12 (.93%)	**2.04 (1.12-3.71)**	28 (2.17%)	**5.10 (3.34-7.78)**
Two or More Races	0	--	0	--	0	--
Asian	33 (7.95%)	**15.73 (10.75-23.0)**	26 (6.27%)	**13.7 (9.00-21.04)**	18 (4.34%)	**10.20 (6.19-16.80)**
Hawaiian/ PI	0	--	0	--	0	--
Other	--	--	0	--	0	--
Decline to answer	2	--	3 (.03%)	--	4 (.04%)	--
Primary language						
English†	165 (.44%)	REF	142 (.38%)	REF	176 (.47%)	REF
Spanish	3 (.08%)	**.18 (.06-.56)**	0	--	16 (.43%)	.90 (.54-1.50)
Other/ Not reported	1 (.11%)	--	7 (.78%)	--	9 (.89%)	--
Encounter type						
Outpatient†	26 (.48%)	REF	41 (.76%)	REF	65 (1.20%)	REF
Emergency	96 (.64%)	1.33 (.87-2.05)	44 (.29%)	**.39 (.25-.59)**	31 (.21%)	**.17 (.11-.26)**
Inpatient discharge	31 (.25%)	**.52 (.31-.88)**	59 (.48%)	**.62 (.42-.93)**	85 (.69%)	**.57 (.41-.79)**

	Overdose *N*= 170		Medication-Assisted Treatment (MAT) *N*= 149		Mortality *N*= 201	
	***N* (% total sample)**	**Relative Risk (95% CI)**	***N* (% total sample)**	**Relative Risk (95% CI)**	***N* (% total sample)**	**Relative Risk (95% CI)**
Day surgery	13 (.29%)	**.29 (.15-.56)**	5 (.05%)	**.07 (.03-.18)**	20 (.22%)	**.18 (.11-.29)**
Payer status						
Private†	40 (.28%)	REF	28 (.20%)	REF	60 (.43%)	REF
Public/Government	73 (.35%)	1.23 (.83-1.80)	88 (.42%)	**2.11 (1.38-3.23)**	122 (.58%)	1.37 (1.00-1.86)
Uninsured	57 (.83%)	**2.93 (1.96-4.39)**	33 (.48%)	**2.42 (1.47-4.01)**	18 (.26%)	.62 (.36-1.04)

† Patients with this characteristic served as the reference group; % of Total Sample is also known as "Absolute Risk"; CI denotes confidence interval; Bold values indicate statistically significant values based on the CI; AYA= Adolescents & Young Adults; AI/AN= American Indian/ Alaska Native; AA=African American

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