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Relationship Between Initial Prescription Opioid Exposure Length and Future Opioid Use Disorder Diagnosis in Opioid Naive Adolescents

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RELATIONSHIP BETWEEN INITIAL PRESCRIPTION OPIOID EXPOSURE LENGTH AND FUTURE OPIOID USE DISORDER DIAGNOSIS IN OPIOID NAÏVE ADOLESCENTS

THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
College of Pharmacy at the University of Kentucky

By

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Lexington, Kentucky

Director: Dr. Patricia Freeman, Professor of Pharmacy Practice and Science

Lexington, Kentucky

2020

ABSTRACT OF THESIS

RELATIONSHIP BETWEEN INITIAL PRESCRIPTION OPIOID EXPOSURE LENGTH AND FUTURE OPIOID USE DISORDER DIAGNOSIS IN OPIOID NAÏVE ADOLESCENTS

Objectives: The long-term risks associated with the use of short-term prescription opioids in opioid naïve adolescents in not well characterized. The purpose of this study was to explore the potential association between the days' supply of the initial prescription opioid exposure and the rates of diagnosed OUD in the subsequent 3-year period. *Methods:* We conducted a retrospective cohort study using a nationwide database of commercially-insured adolescents aged 12-17 at the time of the index opioid fill. A multivariable Cox Proportional Hazard regression model was developed to analyze the association of interest while accounting for known risk factors for the development of OUD. *Results:* Results of the Cox Proportional Hazard analysis showed no significant differences in the risks of future OUD diagnosis between any of the days' supply groups. *Conclusions:* In this commercially-insured, opioid naïve adolescent population, there was no significant association between the days' supply of the initial opioid prescription the rate of OUD diagnosis in the subsequent 3-year period.

KEYWORDS: Opioid, adolescent, OUD, opioid use disorder, days' supply

Eric Lindahl

May 12, 2020

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CHAPTER 1. INTRODUCTION

As the opioid crisis continues to grip the nation, there remains a need to better understand the risks of opioid use and the pathways that lead to opioid use disorder (OUD). OUD, previously classified as 'opioid abuse' or 'opioid dependence', is a mental disorder included in the most recent Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[1] It is defined by the American Psychiatric Association as 'a problematic pattern of opioid use that causes significant impairment or distress'.[2] Diagnosis is based on an 11 point questionnaire about characteristics of opioid use, lifestyle impact, and indicators of opioid tolerance and withdrawal.[1] The presence of two indicators qualifies a patient for a OUD diagnosis, with 'mild' severity. 'Moderate' and 'severe' OUD diagnoses occur with the presence of four and six indicators respectively.[3] OUD affects a significant number of people in the United States, as well as the rest of the world. According to the U.S. Centers for Disease Control and Prevention (CDC), an estimated 2.1 million Americans had OUD in 2016.[2] An OUD diagnosis is associated with an increase in the rates of patient morbidity and mortality. Patients with OUD have higher rates of acute hospitalization, emergency department visits, and opioid related complications, as well as increased healthcare costs.[4,5] The risk of death is also significantly increased, with mortality rates up to 20 times higher than that of the general population.[6] Furthermore, patients with OUD who use opioids intravenously place themselves at increased risk for serious comorbidities such as bacterial endocarditis, HIV, and hepatitis.[4]

It has been found that many patients with OUD had their initial exposure to opioids through opioids prescribed to them by a medical professional, often for acute pain.[7,8] As the risks of prescription opioid use became better understood, there were increased efforts to develop guidelines aimed at reducing opioid prescribing. This focus has led to reductions in the amount of prescription opioids dispensed. Since 2011, there has been an estimated 43% decrease in opioid analgesic prescription volume, in morphine milligram equivalents (MME). However, these medications continue to be widely prescribed and their use remains well above pre-2000 levels.[9,10] The CDC estimates there were 58 opioid prescriptions written per 100 Americans in 2017, with 46 people dying every day from prescription opioid-related overdoses.[11,12] Additionally, the IQVIA Institute estimates that

acetaminophen/hydrocodone combination medications were the fifth most dispensed class of medications the US in 2018.[10] These statistics indicate that opioid use in the United States is still high, and reiterate the importance of finding ways to reduce the incidence of OUD and opioid-related harm.

Many patient characteristics have been shown to predispose a patient to developing OUD. A history of a substance use disorder (SUD) and certain mental health diagnoses, such as psychotic disorders, personality disorders and anxiety disorders, are associated with an increased risk of developing OUD.[6,13] Additionally, indicators of economic disadvantage have also been associated with the development of OUD, including a lack of insurance, unemployment, and income.[14] Furthermore, male gender, Caucasian ethnicity, age at first opioid exposure, single marital status, and poor self-reported health have also been associated with OUD.[13,15–18] Genetics may also play a role in predisposition to OUD, however this is less well understood.[19]

It is also important to understand the characteristics of the initial opioid exposure that are associated with OUD, and possible indicators of OUD such as the transition from acute to chronic use. Since many patients with OUD were initially exposed to opioids through a legitimate prescription, these correlations are important in developing clinical guidelines and best practices.[20] Various prescription characteristics have been associated with long term opioid use and OUD, including higher daily opioid dose (in Morphine Milligram Equivalents; MME), the use of long acting or extended release opioids, refill count, and increasing days' supply of the initial prescription.[13,20–24] Interestingly, multiple retrospective studies have found that the length of the initial opioid prescription was a more important factor than opioid dose when predicting the risk of future OUD.[8,21,25] Guidelines from the CDC suggest that treatment durations of 3 days or less will often be sufficient to treat acute pain, with treatment durations of 7 days or more rarely being necessary.[20,26] Other research suggests that the risks of transitioning from acute to chronic opioid use begin to increase starting with the third day of opioid therapy, and rise sharply after the fifth and thirty first days of therapy.[27]

While an increasing duration of the initial opioid prescription may increase the risk of developing OUD, shorter prescriptions may still pose significant risk. It is known that

prolonged opioid exposure puts patients at risk for OUD due to the risks of physical dependence, which increase sharply after 5 days of exposure.[20] However, initial opioid exposures of less than 5 days may also place patients at risk of future OUD, but for a different reason. Regardless of the length of the initial exposure, the prescribed opioid may be a patient's first experience with a mind-altering drug. The pleasurable feelings associated with opioids may cause patients to seek out these drugs, despite a lack of physical dependence. It has been found that adolescents with little to no prior experience with illicit drugs are at an increased risk for future opioid misuse, when compared to their peers with prior exposure.[28] This seems to support the idea that the mind-altering effects of the opioid may be more profound in those with no prior exposure to mind altering drugs. It has also been found that the risks of future opioid misuse may be higher in adolescents who, at baseline, strongly disapprove of illegal drug use.[28] While these patients may avoid exposure to opioids via illicit means, this barrier to is removed when the initial exposure is via a legitimate prescription. This widens the spectrum of at-risk patients to include those who would not otherwise have been exposed to opioids. This data provides evidence for the claim that all lengths of initial exposures may be dangerous, but the reasoning for the transition to OUD may differ based on the length of the initial exposure.

Adolescents (aged 12-17) are a subset of the population that is often exposed to opioids as well. Adolescents commonly experience procedures in which opioids are commonly prescribed, such as dental work, surgery, and sports injuries, which may place them at higher risk for opioid related problems in the future.[29–33] By high school graduation, an estimated 25% of adolescents have been exposed to prescription opioids through either medical or nonmedical means.[34] No other illicit substance is abused more prevalently in the 12-17 age group, aside from marijuana.[35] While adolescents share many of the same OUD risk factors with adults, factors such as prior exposure to illicit substances, motivations for opioid use, social pressures, and neurologic development may differ between the two groups. Therefore, it is important to study these populations separately. As mentioned previously, a lack of prior exposure to mind altering substances may predispose patients to future OUD, even after a single opioid exposure. This risk may disproportionately affect adolescents, as they are less likely to have prior experience with illicit substances or alcohol. Another difference between adults and adolescents are the

varying motivations for using opioids nonmedically. One survey based study found that adults were 42% more likely than adolescents to report abusing opioids in an attempt to relieve physical pain.[14] In contrast, another survey based study found that high school seniors were more likely to report using opioids nonmedically to 'relax' or 'get high.'[36] Additionally, the decision-making systems of the adolescent brain are less developed than those in adults. While the areas of the brain that handle feelings of reward and pain are well developed by the time of adolescence, the areas involved in decision-making and judgement are not fully developed until the mid-twenties.[37] Since the reward system of the adolescent brain is intimately involved in drug use, this differentiates them from adults. These factors, coupled with the extensive peer pressure and desire to fit in, could affect the transition from opioid use to OUD in adolescents.[37]

Both governmental and non-governmental bodies have recognized the potential link between days' supply and the risks of chronic opioid use and future OUD and have worked to place limits on the length of initial opioid prescriptions. Since 2016 when the first legislation was passed in Massachusetts, at least 33 states have adopted some type of opioid prescription limitations.[38] The legislation varies in the method used to restrict initial opioid prescriptions. Methods include limiting the days' supply, limiting the maximum opioid dose (MME), and directing other entities to develop these limitations (such as a state health organization or provider regulatory board). Most commonly, legislation creates statutory limits on the maximum days' supply of the initial opioid prescription. These limits vary between 3 and 14 days, with the most common days' supply limit being 7 days.[38] Non-governmental organizations have also implemented policies to restrict the days' supply of the initial opioid fill, with both CVS and Walmart restricting the filling of initial acute opioid prescriptions to a 7 day supply.[39,40] Despite these limitations, there are often exceptions to these rules, such as the treatment of chronic pain, cancer, or palliative care.[38] Additionally, these restrictions can often be overruled based on the professional judgement of the provider, often requiring explicit documentation of the exception in the patient's medical record. Some states have also taken steps to further limit access to opioids by adolescents, and have developed limits specifically for this population.[38] These laws may extend limits on opioid prescriptions beyond the initial fill, or include other requirements such as mandatory counseling of the minor and/or guardian on the risks of opioid use.

Due to the relatively new implementation of these laws, it is too early to tell which days' supply limit, if any, will lead to reductions in OUD. It is also unclear which days' supply, if any, increases an adolescent's risk for developing OUD. As more states move to implement these laws, further research into the effect of days' supply on the risks of future OUD can help inform policymakers on overall effective approaches and whether or not the adolescent population should be treated differently than adults when considering such legislation.

While there is research describing potential factors influencing the risks of future OUD in adolescents, the effect of days' supply is less well understood. The majority of studies looking at this age group utilize self-reported questionnaires or geographically homogenous populations. Furthermore, relevant studies that do utilize claims data to study long term opioid misuse do not focus specifically on the adolescent population. Further analysis of this topic using nationwide claims data may help better inform recommendations on limiting the length of OUD prescriptions in adolescents. The main objective of this study is to determine if there is an association between the days' supply of the index opioid fill and the rate of future OUD diagnosis in adolescents. We hypothesize that the rates of diagnosed OUD will begin to significantly increase in patients receiving an index opioid prescription of longer than 7 days. Secondary objectives for this study are to determine the prevalence of OUD diagnosis in the population, the average MME per day of the index prescription, and the average days' supply of the initial prescription. These statistics will help better describe characteristics of the initial opioid exposure in this population.

CHAPTER 2. METHODS

2.1 Data Source

This study used deidentified health claims from a large commercially insured population of about 23 million patients for the period of 2008-2017. Patients are demographically representative of the US population with respect to gender and age, and representative of the commercially-insured population on all other measurable characteristics.

2.2 Study Population

All patients with the following characteristics were included in the analysis: (1) at least one opioid prescription between January 1st 2008 and December 31st 2017 as identified using Generic Product Identifier (GPI) codes beginning with '65' (2) at least 6 months of continuous enrollment without an opioid prescription before the index fill, and (3) between the ages of 12 and 17 at the time of the index opioid prescription. Patients with the following characteristics were excluded from the analysis: (1) patients whose first prescription was for a buprenorphine product, (2) patients with a cancer diagnosis in the 6 month lookback period, (3) patients whose first opioid fill was for a Schedule V opioid, (4) patients with a diagnosis of OUD prior to their first opioid fill, (5) patients with an initial opioid prescription days' supply of more than 14 days, and (6) patients whose demographic information was incomplete or invalid. Patients whose index opioid fill was for a buprenorphine product were excluded from the analysis as buprenorphine containing medications are often used in the treatment of OUD. While buprenorphine containing products have demonstrated some efficacy in the treatment of pain, their use is widely popular in medication assisted treatment (MAT) for OUD.[41] To avoid the possibility of the results being affected by missing or incorrectly coded OUD diagnoses, these patients were excluded from the analysis. Consistent with other studies, patients with a cancer diagnosis in the 6-month lookback period were also excluded. Patients whose index opioid fill was for a Schedule V opioid were excluded from the analysis as this class of opioids, which includes medications such as atropine-diphenoxylate and low potency codeine-containing cough syrups, are typically used to treat conditions other than pain. Finally,

since the focus of this study is the effects of acute opioid exposure, patients with initial prescriptions of longer than 14 days were excluded.

2.3 Outcome

Patients were followed from the date of their first opioid prescription until insurance disenrollment, OUD diagnosis, 3 years of continuous follow up, or the end of the dataset period, whichever came first (Figure 2.1). Consistent with previous studies, OUD was defined as a patient with any ICD-9 or ICD-10 diagnosis code for opioid dependence or opioid abuse in any diagnosis field of the claim (Appendix A).[8]

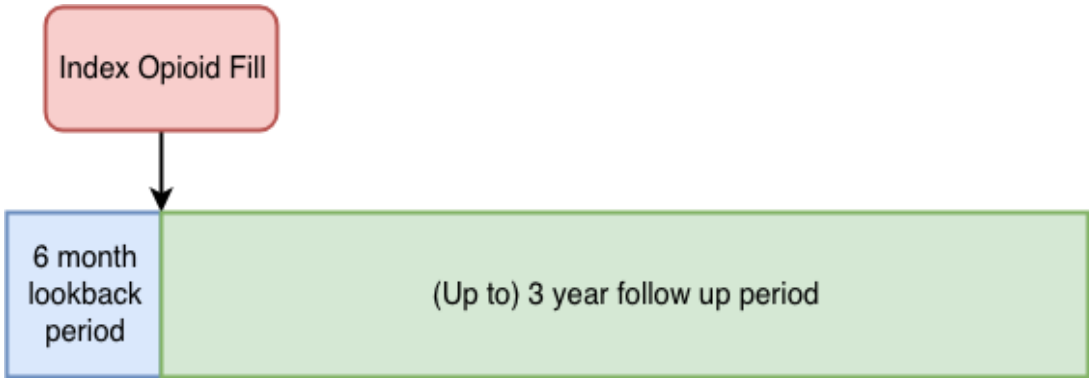
Using the days' supply of the first prescription opioid fill, patients were divided into categories based on common days' supply limitations enacted by states (1-3 days, 3-4 days, 5-7 days, and 8-14 days). MME per day was calculated by multiplying the daily dose (in milligrams) of the prescription by the MME conversion factor. Conversion factors were gathered from the Centers for Medicare and Medicaid Services (CMS).[42] A conversion factor for propoxyphene-containing products was not included in the resource from CMS, and was gathered from another source.[43] 90 MME per day was chosen as the cutoff for a 'high dose' opioid, to create a binary variable for inclusion into the statistical model. This threshold was chosen based on the CDC's recommendation that dosages over 90 MME/day should be avoided, as they can increase the risk of an opioid overdose death by a factor of ten.[7,44] To account for patients with comorbid psychiatric conditions that could predispose them to OUD, a binary variable was created for the presence of these conditions. A search was performed for psychotic, anxiety, and personality disorders using ICD-9 and ICD-10 diagnosis (Appendix B). If the patient was found to have a diagnosis code for any of these conditions during the study period, they were included in the psychiatric subgroup.

2.4 Statistical Analysis

A multivariable Cox-proportional hazard regression model was developed to determine the association between the days' supply of the index opioid prescription on the likelihood of an OUD diagnosis in the subsequent 3 year (1,095 days) follow up period. Covariates for the days' supply group, age at index opioid fill, gender, race, MME per day,

socioeconomic status, and presence of comorbid psychiatric disorders were included in the model. These covariates were chosen due to their previously described association with OUD. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary NC). Since this study utilized de-identified patient data, institutional review board approval was not required.

Figure 2.1: Study Timeline



CHAPTER 3. RESULTS

3.1 Demographics

After applying inclusion and exclusion criteria, 284,514 patients who met study criteria were identified (Figure 3.1). Table 3.1 provides a summary of patient demographics. Patients were an average of 15.3 (±1.58) years of age and similarly divided by gender. Patients in the 16-17 age group accounted for 156,723 (55.1%) of opioid prescriptions. The vast majority (79.6%) were white and 13.4% had a psychiatric disorder diagnosis. Table 3.2 summarizes the characteristics of index opioid prescriptions. The two most common opioids found in the index prescriptions were hydrocodone and codeine containing products, which accounted for 174,484 (61.3%) and 51,337 (18.0%) of prescriptions, respectively. Prescriptions of 3 days were the most common in the study population, accounting for 79,459 (27.9%) of prescriptions. After assignment into groups based on the days' supply of the initial prescription, the most common category was 1-3 days, which accounted for 180,326 (63.4%) patients. The least common category was 8-14 days, which accounted for only 20,647 (7.3%) of prescriptions. The average daily dose of the index opioid fills was 37.1 (± 21.8) MME with few (3.5%) dispensed that were over 90 MME daily. Overall, during the 3 year follow up period, OUD was diagnosed in 423 (0.15%) patients in the study population. Among patients who were diagnosed with OUD within 3 years of their index opioid fill, the mean time to diagnosis was 473 days (~1.3 years).

3.2 Statistical Analysis

Results of the Cox Proportional Hazard analysis (Table 3.3) showed no significant differences in the risks of future OUD diagnosis between any of the days' supply groups. As expected, male gender, increasing age, and the presence of psychiatric disorder diagnoses were associated with increased risk of an OUD diagnosis within 3 years of the index opioid fill. No significant differences in the risk of future OUD diagnosis was seen among race, year of index opioid fill, indicators of income, or whether or not the daily MME was considered 'high dose'. Survival curves were generated for overall survival (Figure 3.2) and survival stratified by days' supply group (Figure 3.3).

Table 3.1: Patient Demographics (n=284,514)

Characteristic	Overall	1-3 Days	4-5 Days	6-7 Days	8-14 Days
	Value (%)	Value (%)	Value (%)	Value (%)	Value (%)
Patient Count	284,514	180,326 (63.4)	59,255 (20.8)	24,286 (8.5)	20,647 (7.3)
Gender					
Male	144,216 (50.7)	90,214 (62.6)	30,741 (21.3)	12,582 (8.7)	10,679 (7.4)
Female	140,298 (49.3)	90,112 (64.2)	28,514 (20.3)	11,704 (8.3)	9,968 (7.1)
Race					
White	226,481 (79.6)	144,713 (63.9)	46,758 (20.7)	18,880 (8.3)	16,130 (7.1)
Hispanic	26,373 (9.3)	15,986 (60.6)	5,810 (22.0)	2,469 (9.4)	2,108 (8.0)
Black	23,322 (8.2)	14,265 (61.2)	4,975 (21.3)	2,190 (9.4)	1,892 (8.1)
Asian	8,338 (2.9)	5,362 (64.3)	1,712 (20.5)	747 (9.0)	517 (6.2)
Household Income					
> 400% Poverty Line	282,695 (99.4)	179,191 (63.4)	58,866 (20.8)	24,123 (8.5)	20,515 (7.3)
< 400% Poverty Line	1,819 (0.6)	1,135 (62.4)	389 (21.4)	163 (9.0)	132 (7.3)
Psychiatric Disorder Diagnosis					
No	246,428 (86.6)	155,866 (63.3)	51,620 (21.0)	21,098 (8.6)	17,844 (7.2)
Yes	38,086 (13.4)	24,460 (64.2)	7,635 (20.1)	3,188 (8.4)	2,803 (7.4)
OUD Diagnosis During Study					
Yes	423 (0.15)	282 (66.7)	80 (18.9)	30 (7.1)	31 (7.3)
No	284,091 (99.9)	180,044 (63.4)	59,175 (20.8)	24,256 (8.5)	20,616 (7.3)

Table 3.2: Index Opioid Fill Characteristics (n=284,514)

Characteristic	**Value**	**Percent (%)**
Days' Supply		
1-3 days	180,326	63.4
4-5 days	59,255	20.8
6-7 days	24,286	8.5
8-14 days	20,647	7.3
Daily MME		
< 90	274,580	96.5
90+	9,917	3.5
Most Prevalent Opioids		
Hydrocodone/Acetaminophen	171,530	60.3
Codeine/Acetaminophen	51,103	18.0
Oxycodone/Acetaminophen	36,322	12.8
Tramadol HCl	8,505	3.0
Oxycodone HCl	5,947	2.1

Table 3.3: Cox-proportional Hazard Regression Model Results (n=284,514)

Characteristic	**Hazard Ratio**	**95% CI**
Days' Supply Group		
1-3	Ref	-
4-5	0.959	0.710 – 1.208
6-7	0.923	0.546 – 1.300
8-14	1.234	0.862 – 1.606
Daily MME		
< 90 MME	Ref	-
90+ MME	0.825	0.290 – 1.360
Gender		
Female	Ref	-
Male	2.15[a]	1.950 – 2.350
Age Group		
12-13	Ref	-
14-15	3.315[a]	2.782 – 3.848
16-17	5.572[a]	5.249 – 6.255
Race		
White	Ref	-
Asian	0.569	-0.239 – 1.377
Black	0.875	0.483 – 1.267
Hispanic	0.661	0.255 – 1.067
Household Income		
> 400% Poverty Line	Ref	-
< 400% Poverty Line	1.376	0.238 – 2.514
Psychiatric Disorder Diagnosis		
No	Ref	-
Yes	10.635[a]	10.434 – 10.836
[a] Statistically Significant with $p < 0.05$		

Figure 3.1: Patient Exclusion Flowchart

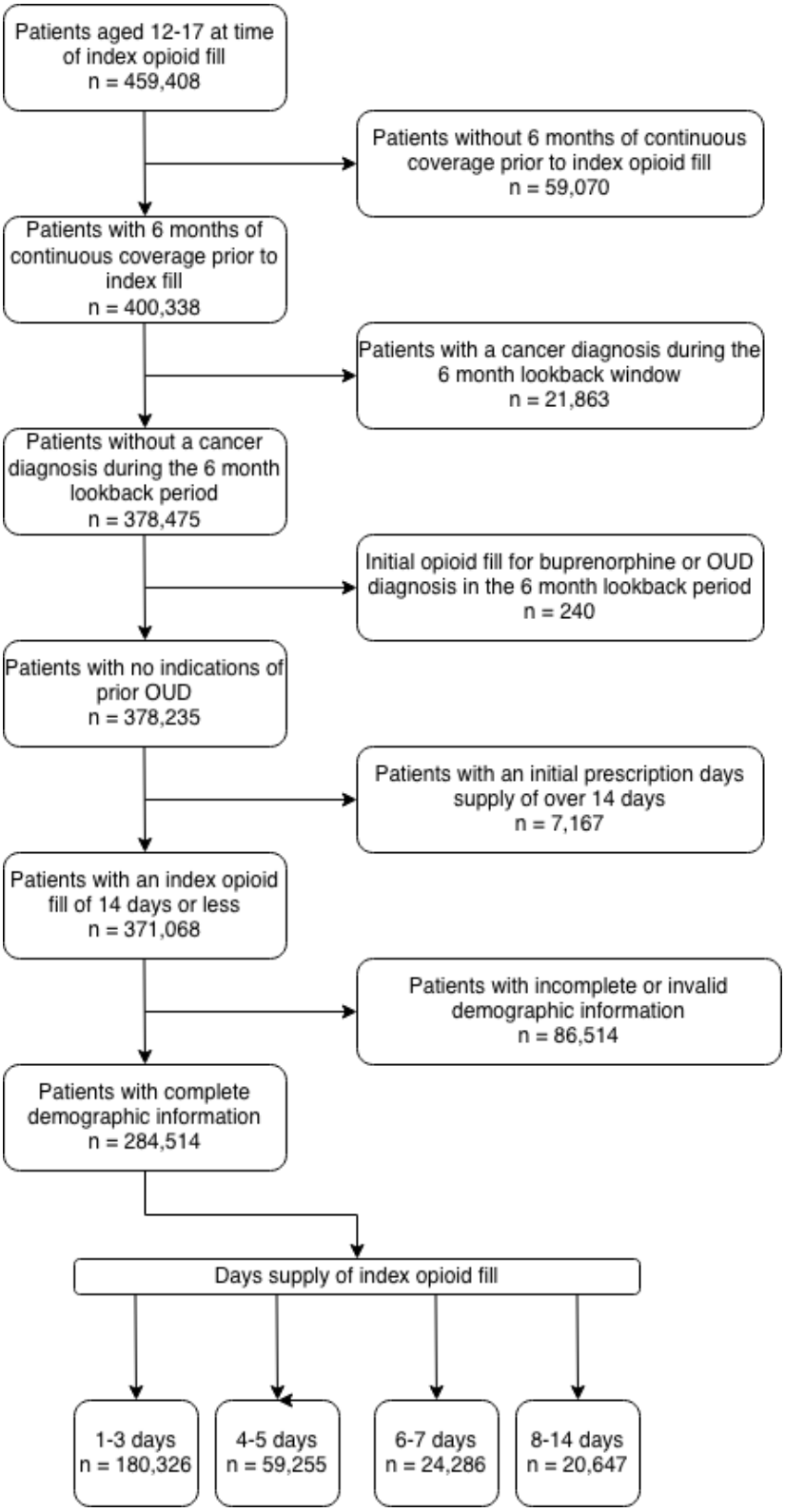


Figure 3.2: Overall Survival Curve (n=423)

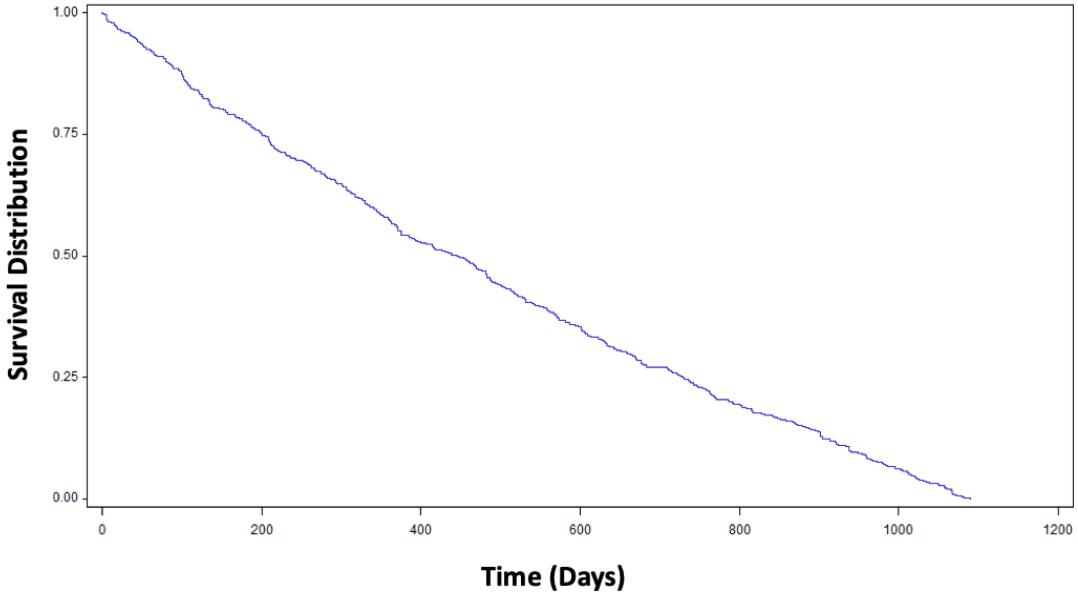
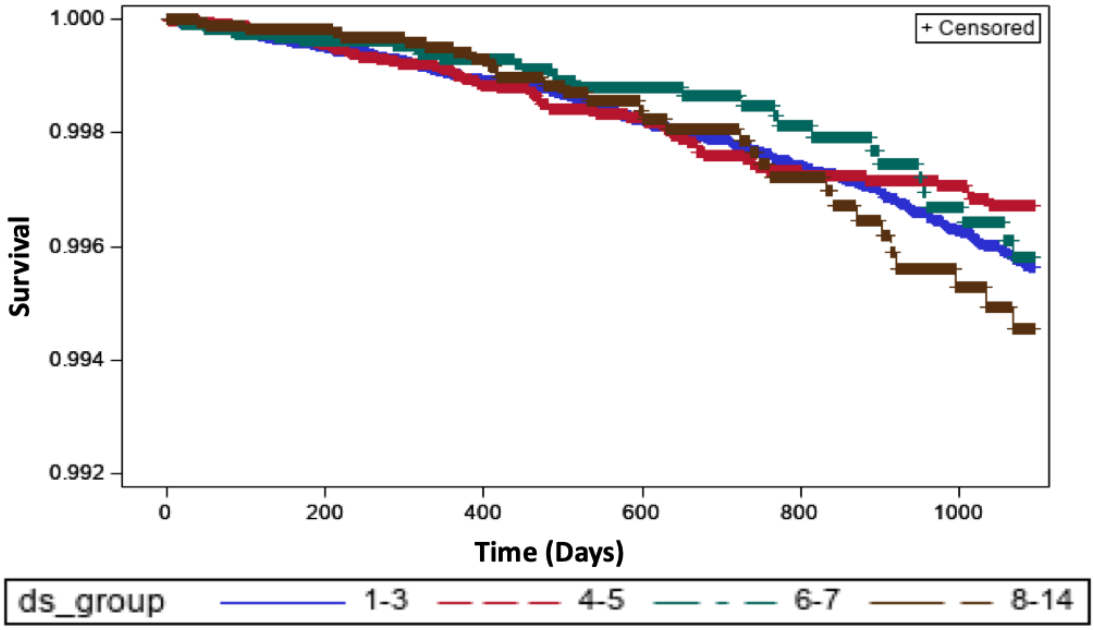


Figure 3.3: Survival Curve Stratified by Days' Supply of the Index Opioid Prescription (n=284,514)



CHAPTER 4. DISCUSSION

4.1 Discussion of Results

In this study of 284,414 privately insured, opioid naïve U.S. adolescents, no association was found between the days' supply of the index opioid prescription and the risk of OUD diagnosis in the subsequent 3-year period. Even for prescriptions of less than 3 days, thought to be too short to cause physical dependence, the risk of future OUD diagnosis is not significantly lower than prescriptions of 8-14 days. While no other study has found an association between days' supply and future OUD diagnosis in adolescents, other studies have found links between days' supply and surrogates of OUD, such as opioid overdose and a transition to long term opioid use. One study of 1.3 million privately insured patients 14 years and older found that the probability of continued opioid use increases steadily with the days' supply of the initial opioid fill, with days' supplies up to >22 days. The study found that, when compared to initial prescriptions of 2 days or less, prescriptions of 5-7 days and 8-10 days increased the chances of long term opioid use by a factor of three and a factor of five, respectively. [8] A second study found a substantial increase in the probability of continued opioid use in opioid naïve adults once the days' supply of the initial prescription reached 6 days, with another substantial increase after 10 days.[27] A third study looking at post-surgical opioid naïve adults found that each additional week of opioid supply increased the risk of future opioid misuse by 20%.[45]

While this finding does not give specific guidance on days' supply limits to states considering statutory limitations on initial opioid prescriptions, these findings may support the consideration of differing limitations on adolescents compared to adults. While other studies in adults show that the risk of OUD diagnoses may increase with days' supply, this data does not support that in adolescents. Rather, it shows that a shorter days' supply is no 'safer' than a longer days' supply in adolescents. While all medications should be prescribed for the lowest possible dose for the shortest duration, prescribers should remain especially cognizant of this for opioids given the state of the opioid epidemic.

Consistent with previous literature, the results also showed that male gender, increased age at exposure, and comorbid psychiatric disorders were associated with an

increased incidence of OUD. In contrast to previous studies, no increase in the incidence of OUD diagnosis was seen in regard to race or indicators of socioeconomic status. High dose opioids (90+ MME) were also not found to increase the risk of a future OUD diagnosis. The findings of OUD diagnosis rates (0.15%) and time to OUD diagnosis (~1.3 years) in this study were lower when compared to a prior study of opioid naïve patients in the post-surgical setting. The study included 146,556 patients age 24 and under, in which opioid misuse was subsequently identified in 0.22% of patients <15 years of age, and 1.25% in patients aged 15-24. The mean time to opioid misuse was 2.39 years in patients <15 years old, and 1.47 years in patients 15-24.[45]

4.2 Limitations

Several limitations must be considered when interpreting these results. First, no control group containing patients without an opioid exposure was included in this study. Due to the difficulty in accounting for the multitude of risk factors that may vary between opioid users and non-opioid users, this element was not pursued in this analysis. The absence of this control group means the baseline rate of OUD diagnosis is unable to be determined in this cohort. Secondly, this dataset only included commercially insured patients. Therefore, uninsured patients and patients covered under Medicaid were not included in this analysis, leaving out a large proportion of opioid users with many risk factors for OUD. Additionally, this study relies on medical coding for OUD diagnosis information and comorbid condition identification, both during the study period and the six-month lookback period. Errors or omissions common with medical coding could affect the results. Due to the nature of claims data, it is impossible to determine if the medications were taken as directed, or even taken at all. Also, prescriptions not run through insurance would not be captured in this dataset. Additionally, this study did not consider characteristics of opioid exposures other than the index fill. This could lead to inter-patient variability in subsequent opioid exposures, which could affect the risks of OUD diagnosis. Also, while this study incorporated a six-month lookback period, a patient may have been exposed to opioids prior to this lookback period, meaning the patient would not truly be opioid naïve. Pain etiology and a patient's history of other substance use disorders were

also not included in this analysis, and this information has been shown to affect the risks of OUD.

4.3 Conclusions

In this commercially-insured, opioid naïve adolescent population, there was no significant association between the days' supply of the initial opioid prescription the rate of OUD diagnosis in the subsequent 3-year period. This data suggests that the risk of future OUD for initial opioid exposures of 1-3 days, thought to be too short to induce physical dependence, are not significantly different than prescriptions lengths of up to 14 days. Extra caution should be taken when prescribing opioids of any duration, especially in patients who are male, older adolescents, and/or have comorbid psychiatric conditions.

APPENDICES

Appendix A: Diagnosis Codes for Opioid Use Disorder

304.00	Opioid type dependence, unspecified
304.01	Opioid type dependence, continuous
304.02	Opioid type dependence, episodic
304.03	Opioid type dependence, in remission
304.70	Combinations of opioid type drug with any other drug dependence, unspecified
304.71	Combinations of opioid type drug with any other drug dependence, continuous
304.72	Combinations of opioid type drug with any other drug dependence, episodic
304.73	Combinations of opioid type drug with any other drug dependence, in remission
305.50	Opioid abuse, unspecified
305.51	Opioid abuse, continuous
305.52	Opioid abuse, episodic
305.53	Opioid abuse, in remission
F11.10	Opioid abuse, uncomplicated
F11.120	Opioid abuse with intoxication, uncomplicated
F11.121	Opioid abuse with intoxication delirium
F11.122	Opioid abuse with intoxication with perceptual disturbance
F11.129	Opioid abuse with intoxication, unspecified
F11.14	Opioid abuse with opioid-induced mood disorder
F11.150	Opioid abuse with opioid-induced psychotic disorder with delusions
F11.151	Opioid abuse with opioid-induced psychotic disorder with hallucinations
F11.159	Opioid abuse with opioid-induced psychotic disorder, unspecified
F11.181	Opioid abuse with opioid-induced sexual dysfunction
F11.182	Opioid abuse with opioid-induced sleep disorder
F11.188	Opioid abuse with other opioid-induced disorder
F11.19	Opioid abuse with unspecified opioid-induced disorder
F11.20	Opioid dependence, uncomplicated
F11.21	Opioid dependence, in remission
F11.220	Opioid dependence with intoxication, uncomplicated
F11.221	Opioid dependence with intoxication delirium
F11.222	Opioid dependence with intoxication with perceptual disturbance
F11.229	Opioid dependence with intoxication, unspecified
F11.23	Opioid dependence with withdrawal
F11.24	Opioid dependence with opioid-induced mood disorder
F11.250	Opioid dependence with opioid-induced psychotic disorder with delusions
F11.251	Opioid dependence with opioid-induced psychotic disorder with hallucinations
F11.259	Opioid dependence with opioid-induced psychotic disorder, unspecified
F11.281	Opioid dependence with opioid-induced sexual dysfunction
F11.282	Opioid dependence with opioid-induced sleep disorder
F11.288	Opioid dependence with other opioid-induced disorder
F11.29	Opioid dependence with unspecified opioid-induced disorder
F11.90	Opioid use, unspecified, uncomplicated
F11.920	Opioid use, unspecified with intoxication, uncomplicated
F11.921	Opioid use, unspecified with intoxication delirium

F11.922	Opioid use, unspecified with intoxication with perceptual disturbance
F11.929	Opioid use, unspecified with intoxication, unspecified
F11.93	Opioid use, unspecified with withdrawal
F11.94	Opioid use, unspecified with opioid-induced mood disorder
F11.950	Opioid use, unspecified with opioid-induced psychotic disorder with delusions
F11.951	Opioid use, unspecified with opioid-induced psychotic disorder with hallucinations
F11.959	Opioid use, unspecified with opioid-induced psychotic disorder, unspecified
F11.981	Opioid use, unspecified with opioid-induced sexual dysfunction
F11.982	Opioid use, unspecified with opioid-induced sleep disorder
F11.988	Opioid use, unspecified with other opioid-induced disorder
F11.99	Opioid use, unspecified with unspecified opioid-induced disorder

Appendix B: Diagnosis Codes for Psychiatric Disorders

Psychotic Disorders	
295.00	Simple type schizophrenia, unspecified
295.01	Simple type schizophrenia, subchronic
295.02	Simple type schizophrenia, chronic
295.03	Simple type schizophrenia, subchronic with acute exacerbation
295.04	Simple type schizophrenia, chronic with acute exacerbation
295.05	Simple type schizophrenia, in remission
295.10	Disorganized type schizophrenia, unspecified
295.11	Disorganized type schizophrenia, subchronic
295.12	Disorganized type schizophrenia, chronic
295.13	Disorganized type schizophrenia, subchronic with acute exacerbation
295.14	Disorganized type schizophrenia, chronic with acute exacerbation
295.15	Disorganized type schizophrenia, in remission
295.20	Catatonic type schizophrenia, unspecified
295.21	Catatonic type schizophrenia, subchronic
295.22	Catatonic type schizophrenia, chronic
295.23	Catatonic type schizophrenia, subchronic with acute exacerbation
295.24	Catatonic type schizophrenia, chronic with acute exacerbation
295.25	Catatonic type schizophrenia, in remission
295.30	Paranoid type schizophrenia, unspecified
295.31	Paranoid type schizophrenia, subchronic
295.32	Paranoid type schizophrenia, chronic
295.33	Paranoid type schizophrenia, subchronic with acute exacerbation
295.34	Paranoid type schizophrenia, chronic with acute exacerbation
295.35	Paranoid type schizophrenia, in remission
295.40	Schizophreniform disorder, unspecified
295.41	Schizophreniform disorder, subchronic
295.42	Schizophreniform disorder, chronic
295.43	Schizophreniform disorder, subchronic with acute exacerbation
295.44	Schizophreniform disorder, chronic with acute exacerbation
295.45	Schizophreniform disorder, in remission
295.50	Latent schizophrenia, unspecified
295.51	Latent schizophrenia, subchronic
295.52	Latent schizophrenia, chronic
295.53	Latent schizophrenia, subchronic with acute exacerbation
295.54	Latent schizophrenia, chronic with acute exacerbation
295.55	Latent schizophrenia, in remission
295.60	Schizophrenic disorders, residual type, unspecified
295.61	Schizophrenic disorders, residual type, subchronic
295.62	Schizophrenic disorders, residual type, chronic
295.63	Schizophrenic disorders, residual type, subchronic with acute exacerbation
295.64	Schizophrenic disorders, residual type, chronic with acute exacerbation
295.65	Schizophrenic disorders, residual type, in remission
295.70	Schizoaffective disorder, unspecified
295.71	Schizoaffective disorder, subchronic
295.72	Schizoaffective disorder, chronic
295.73	Schizoaffective disorder, subchronic with acute exacerbation

295.74	Schizoaffective disorder, chronic with acute exacerbation
295.75	Schizoaffective disorder, in remission
295.80	Other specified types of schizophrenia, unspecified
295.81	Other specified types of schizophrenia, subchronic
295.82	Other specified types of schizophrenia, chronic
295.83	Other specified types of schizophrenia, subchronic with acute exacerbation
295.84	Other specified types of schizophrenia, chronic with acute exacerbation
295.85	Other specified types of schizophrenia, in remission
295.90	Unspecified schizophrenia, unspecified
295.91	Unspecified schizophrenia, subchronic
295.92	Unspecified schizophrenia, chronic
295.93	Unspecified schizophrenia, subchronic with acute exacerbation
295.94	Unspecified schizophrenia, chronic with acute exacerbation
295.95	Unspecified schizophrenia, in remission
297.0	Paranoid state, simple
297.1	Delusional disorder
297.2	Paraphrenia
297.3	Shared psychotic disorder
297.8	Other specified paranoid states
297.9	Unspecified paranoid state
298.0	Depressive type psychosis
298.1	Excitative type psychosis
298.2	Reactive confusion
298.3	Acute paranoid reaction
298.4	Psychogenic paranoid psychosis
298.8	Other and unspecified reactive psychosis
298.9	Unspecified psychosis
F20.0	Paranoid schizophrenia
F20.1	Disorganized schizophrenia
F20.2	Catatonic schizophrenia
F20.3	Undifferentiated schizophrenia
F20.5	Residual schizophrenia
F20.81	Schizophreniform disorder
F20.89	Other schizophrenia
F20.9	Schizophrenia, unspecified
F21	Schizotypal disorder
F22	Delusional disorders
F23	Brief psychotic disorder
F24	Shared psychotic disorder
F25.0	Schizoaffective disorder, bipolar type
F25.1	Schizoaffective disorder, depressive type
F25.8	Other schizoaffective disorders
F25.9	Schizoaffective disorder, unspecified
F28	Other psychotic disorder not due to a substance or known physiological condition
F29	Unspecified psychosis not due to a substance or known physiological condition
Anxiety Disorders	
300.00	Anxiety state, unspecified
300.01	Panic disorder without agoraphobia
300.02	Generalized anxiety disorder

300.09	Other anxiety states
300.10	Hysteria, unspecified
300.11	Conversion disorder
300.12	Dissociative amnesia
300.13	Dissociative fugue
300.14	Dissociative identity disorder
300.15	Dissociative disorder or reaction, unspecified
300.16	Factitious disorder with predominantly psychological signs and symptoms
300.19	Other and unspecified factitious illness
300.20	Phobia, unspecified
300.21	Agoraphobia with panic disorder
300.22	Agoraphobia without mention of panic attacks
300.23	Social phobia
300.29	Other isolated or specific phobias
F40.00	Agoraphobia, unspecified
F40.01	Agoraphobia with panic disorder
F40.02	Agoraphobia without panic disorder
F40.10	Social phobia, unspecified
F40.11	Social phobia, generalized
F40.210	Arachnophobia
F40.218	Other animal type phobia
F40.220	Fear of thunderstorms
F40.228	Other natural environment type phobia
F40.230	Fear of blood
F40.231	Fear of injections and transfusions
F40.232	Fear of other medical care
F40.233	Fear of injury
F40.240	Claustrophobia
F40.241	Acrophobia
F40.242	Fear of bridges
F40.243	Fear of flying
F40.248	Other situational type phobia
F40.290	Androphobia
F40.291	Gynephobia
F40.298	Other specified phobia
F40.8	Other phobic anxiety disorders
F40.9	Phobic anxiety disorder, unspecified
F41.0	Panic disorder [episodic paroxysmal anxiety] without agoraphobia
F41.1	Generalized anxiety disorder
F41.3	Other mixed anxiety disorders
F41.8	Other specified anxiety disorders
F41.9	Anxiety disorder, unspecified
Personality Disorders	
301.0	Paranoid personality disorder
301.10	Affective personality disorder, unspecified
301.11	Chronic hypomanic personality disorder
301.12	Chronic depressive personality disorder
301.13	Cyclothymic disorder
301.20	Schizoid personality disorder, unspecified

301.21	Introverted personality
301.22	Schizotypal personality disorder
301.3	Explosive personality disorder
301.4	Obsessive-compulsive personality disorder
301.50	Histrionic personality disorder, unspecified
301.51	Chronic factitious illness with physical symptoms
301.59	Other histrionic personality disorder
301.6	Dependent personality disorder
301.7	Antisocial personality disorder
301.81	Narcissistic personality disorder
301.82	Avoidant personality disorder
301.83	Borderline personality disorder
301.84	Passive-aggressive personality
301.89	Other personality disorders
301.9	Unspecified personality disorder
F60.0	Paranoid personality disorder
F60.1	Schizoid personality disorder
F60.2	Antisocial personality disorder
F60.3	Borderline personality disorder
F60.4	Histrionic personality disorder
F60.5	Obsessive-compulsive personality disorder
F60.6	Avoidant personality disorder
F60.7	Dependent personality disorder
F60.81	Narcissistic personality disorder
F60.89	Other specific personality disorders
F60.9	Personality disorder, unspecified

BIBLIOGRAPHY

1. American Psychiatric Association. DSM-5 Criteria for Diagnosis of Opioid Use Disorder. 2013. https://www.asam.org/docs/default-source/education-docs/dsm-5-dx-oud-8-28-2017.pdf. Accessed January 10, 2020.
2. U.S Centers for Disease Control. Assessing and Addressing Opioid Use Disorder (OUD). https://www.cdc.gov/drugoverdose/training/oud/accessible/index.html. Accessed March 5, 2020.
3. U.S. Department of Veterans Affairs. A VA Clinician's Guide to Identification and Management of Opioid Use Disorder (2016). 2016. https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Opioid_Use_Disorder_Educational_Guide.pdf. Accessed February 14, 2020.
4. Turner, Carla C ; Fogger, Susanne A ; Frazier, Sandra L. Opioid Use Disorder: Challenges During Acute Hospitalization. *The Journal for Nurse Practitioners*. 2018;14(2):61-67.
5. White AG, Birnbaum HG, Mareva MN, et al. Direct Costs of Opioid Abuse in an Insured Population in the United States. *JMCP*. 2005;11(6):469-479. doi:10.18553/jmcp.2005.11.6.469
6. Hser Y-I, Evans E, Grella C, Ling W, Anglin D. Long-Term Course of Opioid Addiction: *Harvard Review of Psychiatry*. 2015;23(2):76-89. doi:10.1097/HRP.0000000000000052
7. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *MMWR Recomm Rep*. 2016;65. doi:10.15585/mmwr.rr6501e1er
8. Shah A, Hayes CJ, Martin BC. Factors Influencing Long-Term Opioid Use Among Opioid Naive Patients: An Examination of Initial Prescription Characteristics and Pain Etiologies. *J Pain*. 2017;18(11):1374-1383. doi:10.1016/j.jpain.2017.06.010
9. Prescription Opioid Data | Drug Overdose | CDC Injury Center. https://www.cdc.gov/drugoverdose/data/prescribing.html. Published August 31, 2018. Accessed November 16, 2018.
10. Medicine Use and Spending in the U.S. - A Review of 2018 and Outlook to 2023. May 2019. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us---a-review-of-2018-outlook-to-2023.pdf?_=1578418464049. Accessed January 7, 2020.
11. Seth P, Scholl L, Rudd RA, Bacon S. Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants — United States, 2015–2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(12):349-358. doi:10.15585/mmwr.mm6712a1
12. U.S. Centers for Disease Control. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes. 2018. https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf. Accessed March 6, 2020.
13. Klimas J, Gorfinkel L, Fairbairn N, et al. Strategies to Identify Patient Risks of Prescription Opioid Addiction When Initiating Opioids for Pain. *JAMA Netw Open*. 2019;2(5). doi:10.1001/jamanetworkopen.2019.3365
14. Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med*. 2017;167(5):293-301. doi:10.7326/M17-0865

15. Han B, Compton WM, Blanco C, Jones CM. Correlates of Prescription Opioid Use, Misuse, Use Disorders, and Motivations for Misuse Among US Adults. *J Clin Psychiatry*. 2018;79(5). doi:10.4088/JCP.17m11973
16. Katz C, El-Gabalawy R, Keyes KM, Martins SS, Sareen J. Risk factors for incident nonmedical prescription opioid use and abuse and dependence: Results from a longitudinal nationally representative sample. *Drug Alcohol Depend*. 2013;132(1-2):107-113. doi:10.1016/j.drugalcdep.2013.01.010
17. McCabe SE, West BT, Morales M, Cranford JA, Boyd CJ. Does early onset of non-medical use of prescription drugs predict subsequent prescription drug abuse and dependence? Results from a national study. *Addiction*. 2007;102(12):1920-1930. doi:10.1111/j.1360-0443.2007.02015.x
18. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain: *Pain*. 2007;129(3):355-362. doi:10.1016/j.pain.2007.02.014
19. Kendler KS, Jacobson KC, Prescott CA, Neale MC. Specificity of Genetic and Environmental Risk Factors for Use and Abuse/Dependence of Cannabis, Cocaine, Hallucinogens, Sedatives, Stimulants, and Opiates in Male Twins. *AJP*. 2003;160(4):687-695. doi:10.1176/appi.ajp.160.4.687
20. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *MMWR Recomm Rep*. 2016;65. doi:10.15585/mmwr.rr6501e1er
21. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ*. 2018;360:j5790. doi:10.1136/bmj.j5790
22. Deyo RA, Hallvik SE, Hildebran C, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naïve Patients: A Statewide Retrospective Cohort Study. *J Gen Intern Med*. 2017;32(1):21-27. doi:10.1007/s11606-016-3810-3
23. Bohnert ASB, Valenstein M, Bair MJ, et al. Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths. *JAMA*. 2011;305(13):1315-1321. doi:10.1001/jama.2011.370
24. Chua K-P, Brummett CM, Conti RM, Bohnert A. Association of Opioid Prescribing Patterns With Prescription Opioid Overdose in Adolescents and Young Adults. *JAMA Pediatr*. 2020;174(2):141-148. doi:10.1001/jamapediatrics.2019.4878
25. Edlund MJ, Martin BC, Russo JE, Devries A, Braden JB, Sullivan MD. The Role of Opioid Prescription in Incident Opioid Abuse and Dependence Among Individuals with Chronic Non-Cancer Pain: The Role of Opioid Prescription. *Clin J Pain*. 2014;30(7):557-564. doi:10.1097/AJP.0000000000000021
26. Mundkur ML, Franklin JM, Abdia Y, et al. Days' Supply of Initial Opioid Analgesic Prescriptions and Additional Fills for Acute Pain Conditions Treated in the Primary Care Setting — United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2019;68(6):140-143. doi:10.15585/mmwr.mm6806a3
27. Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(10):265-269. doi:10.15585/mmwr.mm6610a1

28. Miech R, Johnston L, O'Malley PM, Keyes KM, Heard K. Prescription Opioids in Adolescence and Future Opioid Misuse. *Pediatrics*. 2015;136(5):e1169-e1177. doi:10.1542/peds.2015-1364
29. Harbaugh CM, Lee JS, Hu HM, et al. Persistent Opioid Use Among Pediatric Patients After Surgery. *Pediatrics*. 2018;141(1):e20172439. doi:10.1542/peds.2017-2439
30. Schroeder AR, Dehghan M, Newman TB, Bentley JP, Park KT. Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and Abuse. *JAMA Intern Med*. 2019;179(2):145-152. doi:10.1001/jamainternmed.2018.5419
31. Veliz P, Boyd CJ, McCabe SE. Nonmedical use of prescription opioids and heroin use among adolescents involved in competitive sports. *J Adolesc Health*. 2017;60(3):346-349. doi:10.1016/j.jadohealth.2016.09.021
32. Veliz PT, Boyd C, McCabe SE. Playing Through Pain: Sports Participation and Nonmedical Use of Opioid Medications Among Adolescents. *Am J Public Health*. 2013;103(5):e28-e30. doi:10.2105/AJPH.2013.301242
33. Dash GF, Wilson AC, Morasco BJ, Feldstein Ewing SW. A Model of the Intersection of Pain and Opioid Misuse in Children and Adolescents. *Clin Psychol Sci*. 2018;6(5):629-646. doi:10.1177/2167702618773323
34. McCabe SE, West BT, Teter CJ, Boyd CJ. Medical and Nonmedical Use of Prescription Opioids among High School Seniors in the United States. *Arch Pediatr Adolesc Med*. 2012;166(9):797-802. doi:10.1001/archpediatrics.2012.85
35. McCabe SE, Veliz P, Schulenberg JE. Adolescent context of exposure to prescription opioids and substance use disorder symptoms at age 35: A national longitudinal study. *Pain*. 2016;157(10):2173-2178. doi:10.1097/j.pain.0000000000000624
36. McCabe SE, Boyd CJ, Cranford JA, Teter CJ. Motives for nonmedical use of prescription opioids among high school seniors in the United States: self-treatment and beyond. *Arch Pediatr Adolesc Med*. 2009;163(8):739-744. doi:10.1001/archpediatrics.2009.120
37. National Institute on Drug Abuse. Principles of Adolescent Substance Use Disorder Treatment: A Research-Based Guide. https://www.drugabuse.gov/publications/principles-adolescent-substance-use-disorder-treatment-research-based-guide/introduction. Published January 2014. Accessed March 6, 2020.
38. National Conference of State Legislatures. Prescribing Policies: States Confront Opioid Overdose Epidemic. http://www.ncsl.org/research/health/prescribing-policies-states-confront-opioid-overdose-epidemic.aspx. Accessed December 27, 2019.
39. CVS Health Fighting National Opioid Abuse Epidemic With Enterprise Initiatives. CVS Health. https://cvshealth.com/newsroom/press-releases/cvs-health-fighting-national-opioid-abuse-epidemic-with-enterprise-initiatives. Accessed November 17, 2018.
40. Walmart Introduces Additional Measures to Help Curb Opioid Abuse and Misuse. https://news.walmart.com/_news_/2018/05/07/walmart-introduces-additional-measures-to-help-curb-opioid-abuse-and-misuse. Accessed November 17, 2018.

41. Aiyer R, Gulati A, Gungor S, Bhatia A, Mehta N. Treatment of Chronic Pain With Various Buprenorphine Formulations: A Systematic Review of Clinical Studies. *Anesthesia & Analgesia*. 2018;127(2):529-538. doi:10.1213/ANE.0000000000002718
42. Centers for Medicare and Medicaid Services (CMS). Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors. 2017. https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf. Accessed February 14, 2020.
43. Vieweg WVR, Lipps WFC, Fernandez A. Opioids and Methadone Equivalents for Clinicians. *Prim Care Companion J Clin Psychiatry*. 2005;7(3):86-88.
44. CDC. Protect patients from opioid overdose. Centers for Disease Control and Prevention. https://www.cdc.gov/vitalsigns/opioids/infographic.html. Published July 6, 2017. Accessed March 22, 2020.
45. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ*. 2018;360:j5790. doi:10.1136/bmj.j5790

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   Blackmer J, Lindahl E, Strahl A, Schadler A, Freeman P. Regulating gabapentin as a drug of abuse: A survey study of Kentucky community pharmacists. *J Am Pharm Assoc*. 2019;59(3):379-382. doi:10.1016/j.japh.2018.12.018

   Lindahl E, Tilton K, Eickholt N, Ferguson-Stegall L. Yoga reduces perceived stress and exhaustion levels in healthy elderly individuals. *Complement Ther Clin Pract.* 2016;24:50-56. doi:10.1016/j.ctcp.2016.05.007

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