University of Cincinnati

Date: 3/23/2016

I, Rachel M Ancona, hereby submit this original work as part of the requirements for the degree of Master of Science in Epidemiology (Environmental Health).

It is entitled:

Prescribed Opioids as an Initial Exposure in Emergency Department Patients Reporting Nonmedical Opioid or Heroin Use

Student's name: **Rachel M Ancona**

This work and its defense approved by:

Committee chair: Kim Dietrich, Ph.D.

Committee member: Michael Lyons, M.D., M.P.H.

Committee member: Marepalli Rao, Ph.D.

UNIVERSITY OF Cincinnati

19735

Prescribed Opioids as an Initial Exposure in Emergency Department Patients Reporting Nonmedical Opioid or Heroin Use

A thesis submitted to the

Graduate School

of the University of Cincinnati

in partial fulfillment of the

requirements for the degree of

MASTER OF SCIENCE

in the Department of Environmental Health,

Division of Epidemiology,

of the College of Medicine

by

Rachel M Ancona

B.S., Biology, University of Cincinnati, 2011

3/28/2016

Committee Chair: Kim Dietrich, PhD

ABSTRACT

The problem of prescription opioid pain reliever misuse and abuse has become a critical public health issue in the United States. Current public health efforts include monitoring patients on courses of opioid pain therapy, treatment interventions for those who are already abusing or misusing opioids, prescription drug monitoring programs aimed at reducing misuse and diversion, and Naloxone distribution programs to save the lives of those who overdose. To date, there has been little definitive research on prescribed opioids as an initial exposure preceding opioid abuse. This study examined the proportion of emergency department patients with a history of opioid abuse who reported their initial exposure as medical (prescribed to them by their doctor for a medical purpose) and, if so reported, how many of those initial prescriptions came from an emergency department (ED). In this cross-sectional study design, ED patients who self-reported nonmedical opioid use were surveyed about their initial opioid exposure, non-opioid substance use prior to initial opioid exposure, and subsequent opioid use including time from initial exposure to nonmedical use. From 59 enrolled subjects, 35 reported their initial opioid exposure as medical (35/59; 59%; 95% confidence interval [CI] 47% to 71%), and of these, 10 reported their initial exposure was from an emergency department (10/35; 29%; 95% CI 16% to 45%). Thirty-one of the 35 medically exposed subjects reported that time from initial exposure to onset of nonmedical use, with a median time from initial medical exposure to onset of nonmedical use was 12 months (interquartile range [IQR] 2 to 36). Most medically exposed subjects (28/35; 80%; 95% CI 65% to 91%) reported non-opioid substance use (illicit substance use) or treatment for non-opioid substance use (alcohol or illicit substance use) prior to, or at the time of, their initial medical exposure. Medically exposed subjects were similar in characteristics, in their non-opioid substance use prior to initial exposure, and subsequent intravenous drug use and opioid overdose. While this preliminary study has a limited sample size and its results are not definitive, the high proportion reporting their initial opioid exposure as medical, and the short

time from that initial medical exposure to onset of nonmedical opioid use, the results support future research into legitimate medical prescriptions as an exposure contributing to incident cases of opioid abuse.

Key Words: prescription drugs, emergency department, opioids, heroin, overdose

Acknowledgements

This project was supported in part by an Institutional Clinical and Translational Science Award, National Institutes of Health (NIH)/National Center for Research Resources (NCRR) grant 8 UL1TR000077-05.

This thesis is part of a collaborative project that has produced two abstract poster presentations (University of Cincinnati Research Week and Society of Academic Emergency Medicine Annual Meeting) and a published manuscript (Annals of Emergency Medicine). Megan Butler, Kim Hart, Christopher Lindsell, and Mike Lyons developed the protocol; Megan Butler, Gillian Beauchamp, and Cyrus Yamin collected the data; Rachel Ancona edited the case report form, built the database, developed analysis plan and conducted the analyses under the guidance of Kim Hart; Megan Butler and Rachel Ancona wrote the manuscript; Erin Winstanley, Shawn Ryan, Richard Ryan, and Andrew Ruffner provided topic specific feedback and guidance; and all authors contributed to editing of the final manuscript.

I wish to thank all of the co-authors on the manuscript for their contribution to this project: Megan M. Butler, BS, Gillian A. Beauchamp, MD, Cyrus K. Yamin, MD, Erin L. Winstanley, PhD, Kimberly W. Hart, MA, Andrew H. Ruffner, MA, LSW, Shawn W. Ryan, MD, MBA, Richard J. Ryan, MD, Christopher J. Lindsell, PhD, and Michael S. Lyons, MD, MPH. I also wish to thank Kimberly W. Hart for statistical input and mentorship, Michael S. Lyons, MD, MPH for guidance and mentorship, and Megan M. Butler, BS, for her considerable contribution to the entire project.

Table of Contents

List of Tables and Figures

Tables:

Figures:

Prescribed Opioids as an Initial Exposure in Emergency Department Patients Reporting Nonmedical Opioid or Heroin Use

INTRODUCTION

The problem of prescription opioid pain reliever misuse and abuse has become a critical public health issue in the United States. Accidental drug overdose overall has become the leading cause of unintentional injury death in the United States, a trend that has been on the rise since 1992. Prescription drugs are a primary source of the problem, causing 22,810 (55%) of the 41,340 total drug overdose deaths in 2011. From these prescription drugs, 16,917 (74%) deaths were related to prescription opioid pain relievers.[1] Prescription opioids are also thought to have contributed to the rise of heroin use, overdose, and death rates.[2] It is estimated that currently over 2.5 million people in the United States suffer from a substance use disorder related to prescription opioids or are addicted to heroin.[3]

Current public health efforts to combat this growing problem include: monitoring patients on courses of opioid pain therapy, treatment interventions for those who are already abusing or misusing opioids, prescription drug monitoring programs aimed at reducing misuse and diversion, and Naloxone distribution programs to save the lives of those who overdose. These measures work towards preventing opioid misuse and diversion, but do not address medical prescriptions for opioid-naïve patients as a potentially significant source of exposure for those who ultimately come to suffer from opioid addiction. The extent to which legitimate medical prescriptions contribute to incident cases of opioid abuse or addiction is unknown.

Emergency departments (EDs) are one of the primary sources of opioid prescriptions. A study released in 2015 reported that 1 in 6 ED patients receives an opioid prescription.[4] With over 130 million emergency department visits a year (2011) and 1 out of 6 of those receiving an opioid

prescription, exploring EDs' contribution to the incident rate of opioid abuse is an important part of understanding the etiology of opioid addiction.[3,5]

Therefore, the goal of this study was to determine if emergency department patients with a history of opioid abuse report their initial exposure as medical (prescribed to them by their doctor for a medical purpose), and, if so, how many of those initial prescriptions came from an ED. We did this through the following specific aims:

Specific Aim 1: Examine the proportion of emergency department patients who self-report nonmedical opioid use (*i.e.*, any use other than prescribed use) whose initial opioid exposure was prescribed as a course of medical treatment and, of these, the proportion that was provided from an emergency department. We hypothesized that at least 5% of enrolled subjects would report their initial prescription as medical and, of those, at least 5% would report their initial prescription was from an emergency department provider. Due to the number of opioids prescribed from emergency departments annually, preliminary evidence of 5% would support further research into legitimate medical prescriptions for opioid-naïve patients as a significant source of exposure for patients who ultimately come to suffer from opioid addiction.

Specific Aim 2: Describe factors for opioid abuse that were present prior to, or at the time of, the initial prescription that may have predicted susceptibility to abuse or misuse, such as: age at time of initial opioid exposure, non-opioid substance use, or non-opioid substance treatment. We additionally described important public health measures of the opioid epidemic reported by our subjects, including: intravenous drug use, opioid overdose, and treatment for opioid use. Lastly, we examined the time from initial opioid exposure to indicators of opioid abuse: first nonmedical use (use to get high or to avoid withdrawal) and onset of regular (using at least once per week for a month or more) nonmedical use.

METHODS

This cross-sectional study consisted of an investigator-administered survey that enrolled a convenience sample of emergency department patients who self-reported nonmedical use of prescription opioids (defined as use of pharmaceutical opioids in a manner other than prescribed) or heroin. This study was approved by the University of Cincinnati Institutional Review Board.

Potential subjects were screened in an urban academic teaching hospital serving a predominately adult population and many of the region's uninsured, with approximately 70,000 encounters each year. Screening was conducted for a period of 4 months, from April through July, 2015. We primarily targeted patients with self-reported heroin or nonmedical opioid use noted in the ED computer chart, patients referred by ED staff as potentially eligible, and patients whose chief complaint included: heroin overdose, withdrawal, or abscess. If no subjects meeting these criteria were present in ED, researchers approached patients ages 18-40 consecutively to inquire if we could ask several questions about medication and drug use; general medication, non-opioid, and opioid questions were mixed as a measure to provide some blinding as to the actual study focus (a "general screen").

Potential subjects who were ≤ 18 years of age and not in police custody were entered into a screening log to track patients approached and reason for approach (type of opioid use for those identified by either ED computer chart or staff, or the general screen). Subjects were eligible if the approach was complete and they were subjectively determined to have the capacity for informed consent. Potential patients identified through the general screen were additionally eligible if they indicated that they had used street opioids or prescription opioids nonmedically (to get high, more than was prescribed, or taken if prescribed to someone else).

Subjects were assured that their responses would not be directly linked to any identifiers. Investigator-administered surveys were conducted privately in patient rooms.

The investigator-administered survey asked subjects about: 1) demographics, 2) initial opioid exposure (type, source, and circumstances surrounding their first opioid exposure), 3) non-opioid substance use: ever used, age of first use, frequency of use, regular use (using at least once a week for the period of 1 month or more), age of first regular use, whether they'd received treatment for that substance and, if so, the age of treatment; 4) opioid substance use: ever used, age of first use, frequency of use, regular use (using at least once a week for the period of 1 month or more), age of first regular use, whether they'd received treatment for that substance and, if so, the age of treatment, 5) reasons for opioid use (both medical and nonmedical): prescribed by doctor to treat medical condition, self-treat for pain or medical condition, to get high, to get high regularly, to avoid withdrawal, to avoid withdrawal regularly, and 6) intravenous drug use and opioid overdose. Medically exposed subjects were asked additional questions about their time from initial exposure to onset of nonmedical opioid: use to get high, use to avoid withdrawal, regular use to get high, and regular use to avoid withdrawal. The survey was designed by the investigative team, which included addiction experts, but it was not validated. All survey information was collected on paper Case Report Forms (CRFs) and entered into a secure database in REDCap.[6]

These results have been previously reported in abstract presentations at the University of Cincinnati Research Week and the Society of Academic Emergency Medicine Annual Meeting, with a full manuscript published in Annals of Emergency Medicine.[7,8,9] For the primary aim, proportions with 95% confidence intervals and the exact method for a one-sample binomial test was used to calculate level of significance. For the secondary aim, differences between the exposure groups were evaluated using Chi-square or Fischer's Exact Test (where appropriate,

for categorical variables) and t-tests (continuous variables). SPSS was used for statistical analyses and to create tables (version 22.0, Armonk, NY; IBM Corp).[10] Figures were created using R (version 3.0.2) and the package Beeswarm (version 0.1.6).[11,12] Missing data were left missing and noted where applicable in the results.

RESULTS

Of 122 potential subjects approached, 79 were eligible, 60 consented, and 59 completed the survey. The 59 subjects qualified for inclusion because of heroin use (42/59; 71%), heroin overdose (12/59; 8%), or nonmedical prescription opioid use (5/59; 8%) (Figure 1). Subjects had a mean age of 34 (SD = 11) and were primarily white (56/59; 95%), non-Hispanic (59/59; 100%), unemployed (34/59; 58%), men (33/59; 56%), who had completed high school or equivalent (37/59; 63%) (Table 1).

Fifty-nine percent of subjects reported medical exposure (35/59; 59%; 95% CI 47% to 71%). A binomial test indicated that the proportion of subjects reporting their opioid exposure as medical of 59% was higher than the estimated proportion of 5% ($p < 0.001$, 1-sided). Of these, 10 reported their medical exposure came from an emergency department (10/35; 29%; 95% CI 16% to 45%). Proportions for all provider types reported are shown in Figure 2. Binomial test also indicated that the proportion of subjects reporting their medical opioid exposure as from an ED of 29% was higher than the estimated proportion of 5% ($p < 0.001$, 1-sided).

Most medically exposed subjects (28/35; 80%; 95% CI 65% to 91%) reported non-opioid substance use (illicit substance use) or treatment for non-opioid substance use (alcohol or illicit substance use) prior to, or at the time of, their initial medical exposure. There were no significant differences identified between initial opioid exposure groups for any potential risk factor (Table 2). Most subjects reported using intravenous drugs (49/59; 83%; 95% CI 72% to

91%) and more than half reported at least one opioid overdose (34/59; 58%; 95% CI 45% to 70%) and treatment for opioid use (32/59; 54%; 95% CI 42% to 67%). There were no significant differences identified between initial opioid exposure groups in any of the reported public health measures (Table 2). Details of prior substance use reported by each exposure group are shown in Table 3.

Thirty-one of the 35 medically exposed subjects reported times from initial exposure to types of nonmedical opioid use. Of these 31 medically exposed subjects, median time from initial prescription to onset of nonmedical use was 12 months (IQR; 2-36) and median time from initial prescription to onset of regular nonmedical use was 24 months (IQR; 2-48) (Table 4). Time from initial medical exposure to first nonmedical use and onset of regular nonmedical use for each patient is shown in Figure 3 (aggregated by type of indicator) and in Figure 4 (aggregated by patient).

DISCUSSION

Although efforts to address the opioid epidemic have thus far focused on preventing misuse or diversion in those who have already been exposed to opioids, there is still much to learn about how people come to abuse opioids in the first place. Prescribing opioids to treat pain is common. Therefore, it is important to understand if medical prescriptions for opioid-naïve patients is a significant source of exposure for those who ultimately come to suffer from opioid addiction and, if so, characterize risk factors to understand which patients would have elevated risk.[4] The aim of this study was to take an initial look at whether legitimate medical prescriptions contribute to incident cases of opioid addiction.

We found that over half of ED patients with a history of nonmedical opioid use reported their initial opioid exposure as medical and, of those, nearly a third were from an ED. Most initial

medical exposures were followed by nonmedical use (use to get high or to avoid withdrawal) of either pharmaceutical opioids or heroin within 6 to 12 months. This short period of time between the initial medical exposure and nonmedical use suggests that the initial medical prescription could have played an important role in incident cases of opioid abuse. While these results are highly preliminary, they are supportive of further research, particularly given the opioid public health crisis and rate of opioid prescribing.[4]

We additionally found that most medically exposed subjects were ostensibly at risk at the time of their initial prescription, due to their high rate of reported non-opioid substance abuse. However, subjects who were exposed to opioids through illicitly obtained pharmaceuticals or heroin were similar in their level of risk at the time of opioid exposure. Characteristically, the exposure groups were also similar. Both groups were primarily young (at the time of initial opioid exposure), white, with limited education, and a history of substance abuse. While these findings are not conclusive, they may suggest that mere exposure, regardless of whether or not it was prescribed, can trigger opioid addiction in those who are high-risk. Future research into characterizing those at high risk for opioid abuse could be used to develop prevention strategies and interventions for patients who are at risk yet require pain treatment.

Limitations of the study include its small sample size and selection bias inherent in recruiting from an urban, academic ED serving many of the underprivileged in the community. Future research with more robust designs, such as a cohort study, recruiting from a more socioeconomically diverse population would be needed to: 1) estimate the true proportion of incident cases of opioid abuse subsequent to a medical exposure, 2) assess the temporal relationship between medical exposure and onset of nonmedical use, 3) capture an accurate baseline at the time of exposure in order to characterize risk, and 4) be generalizable to the population of opioid-naïve patients seeking treatment for pain.

In summary, the high proportion of nonmedical opioid users reporting their initial exposure as medical and the short time from initial exposure to onset of nonmedical use, provide evidence that exposure to opioids via medical provider, including those from emergency departments, is a phenomenon requiring more extensive study as a potential exposure in the etiology of opioid abuse. More conclusive research is needed to develop prevention and intervention strategies for opioid-naïve pain patients at high risk for opioid abuse, which could subsequently result in the reduction incident cases of prescription opioid abuse and heroin addiction, as well as subsequent opioid overdose and death rates.

Table 1. Characteristics of enrolled subjects

Characteristics	(N=59)	
Age—Mean (SD)	34	(11)
Sex—n (%)		
Male	33	(58)
Female	24	(42)
Race—n (%)		
White/Caucasian	56	(95)
Black/African American	3	(5)
Current residence type—n (%)		
Own or rent	39	(66)
Homeless or Drop-In Center	11	(19)
Transient, stay where you can	6	(10)
Supported or transitional housing	2	(3)
Addictions treatment center	1	(2)
Mental health treatment center	0	(0)
Currently lives with—n (%)		
Family and roommates	32	(54)
Lives alone	16	(27)
Lives with Family	10	(17)
Unknown	1	(2)
Highest level of education—n (%)		
High school diploma or GED	23	(39)
Less than high school	22	(37)
Some college	10	(17)
2 year degree / trade school	3	(5)
4 year degree	1	(2)
Current work status—n (%)		
Unemployed	34	(58)
Employed full or part-time	16	(27)
Disabled	7	(12)
Retired	1	(2)
Employed and disabled	1	(2)

**One subject was missing age (n=58)*

Table 2. Differences between medically exposed and non-medically exposed subjects, with 95 % confidence intervals and p-values (N=59).

	Non-Medical (n=24)	Medical (n=35)	Diff.	95% CI Lower	95% CI Upper	P-value
Characteristics						
Age – Mean (SD)	31 (11)	37 (11)	6	0	11	0.053
Male – n (%)	11 (48)	22 (65)	(17)	(-9)	(43)	0.205
White – n (%)	23 (96)	33 (94)	(-2)	(-13)	(10)	0.790
High school / equivalent – n (%)	14 (58)	23 (66)	(7)	(-18)	(33)	0.565
Unemployed – n (%)	15 (63)	28 (80)	(18)	(-6)	(41)	0.152
Potential risk factors						
Age at time of exposure – Mean (SD)	19 (7)	23 (12)	4	-2	9	0.162
Non-opioid substance use – n (%)	22 (92)	27 (77)	(-15)	(-32)	(3)	0.144
Regular non-opioid substance use – n (%)	13 (54)	18 (51)	(-3)	(-29)	(23)	0.836
Treated for non-opioid substance use – n (%)	1 (4)	4 (11)	(7)	(-6)	(21)	0.639
Public health measures of opioid use – n (%)						
Heroin use	23 (96)	31 (89)	(-7)	(-20)	(6)	0.639
IV Drug use	19 (79)	30 (86)	(7)	(-13)	(27)	0.725
Opioid overdose (heroin or pharmaceutical)*	13 (54)	21 (60)	(6)	(-20)	(32)	0.656
Heroin overdose	13 (54)	18 (51)	(-3)	(-29)	(23)	0.836
Pharmaceutical opioid overdose	0 (0)	5 (14)	(43)	(27)	(59)	0.073
Received treatment for opioid use	16 (67)	16 (46)	(-21)	(-46)	(4)	0.113

**Subjects could have reported both heroin overdose and pharmaceutical opioid overdose*

Table 3. Proportions for individual risk factors of opioid abuse (N=59)

	Initial Opioid Exposure			
	Non Medical (n=24)		Medical (n=35)	
Potential Risk Factor	**n**	**(%)**	**n**	**(%)**
Non-opioid substance use	22	(92)	27	(77)
Marijuana	21	(88)	25	(71)
Cocaine	11	(46)	9	(26)
Methamphetamines	2	(8)	2	(6)
Sedatives	6	(25)	4	(11)
Regular non-opioid substance use	13	(54)	18	(51)
Marijuana	13	(54)	13	(37)
Cocaine	3	(13)	4	(11)
Sedatives	2	(8)	3	(9)
Treatment for non-opioid substance	1	(4)	4	(11)
Alcohol	0	(0)	2	(6)
Marijuana	0	(0)	2	(6)
Cocaine	1	(4)	0	(0)

Table 4. Time in months from initial exposure to indicators of opioid abuse (N=31)

		Time (months)	
Indictors of opioid abuse	**No. Reported**	**Median**	**(IQR)**
Onset nonmedical use			
to get high	25	6	(2-36)
to avoid withdrawal	26	18	(2-38)
Onset regular* nonmedical use			
to get high	24	12	(2-36)
to avoid withdrawal	27	24	(2-48)

**Regular nonmedical use was defined at use at least for a week for a period of 1 month or more.*

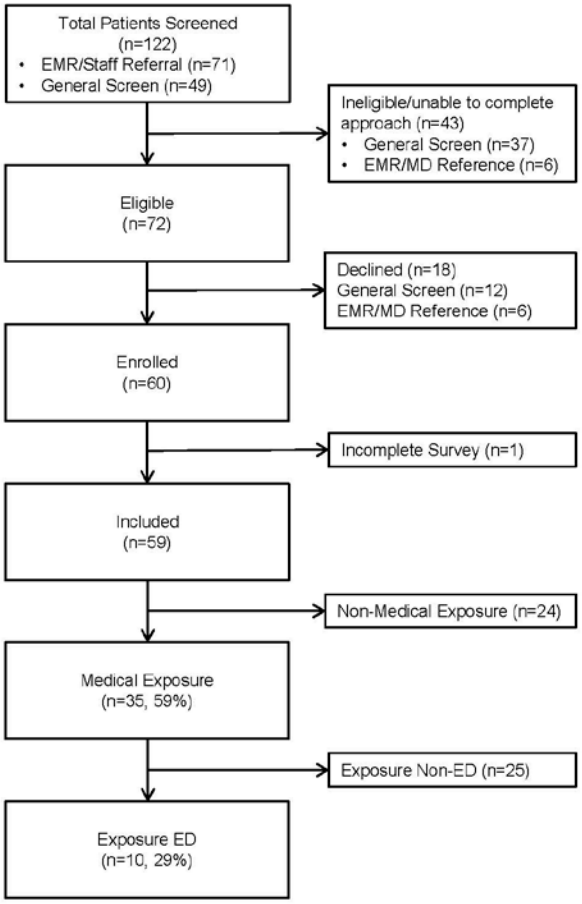

Figure 1. Flow chart of study enrollment and primary outcomes (N=122)

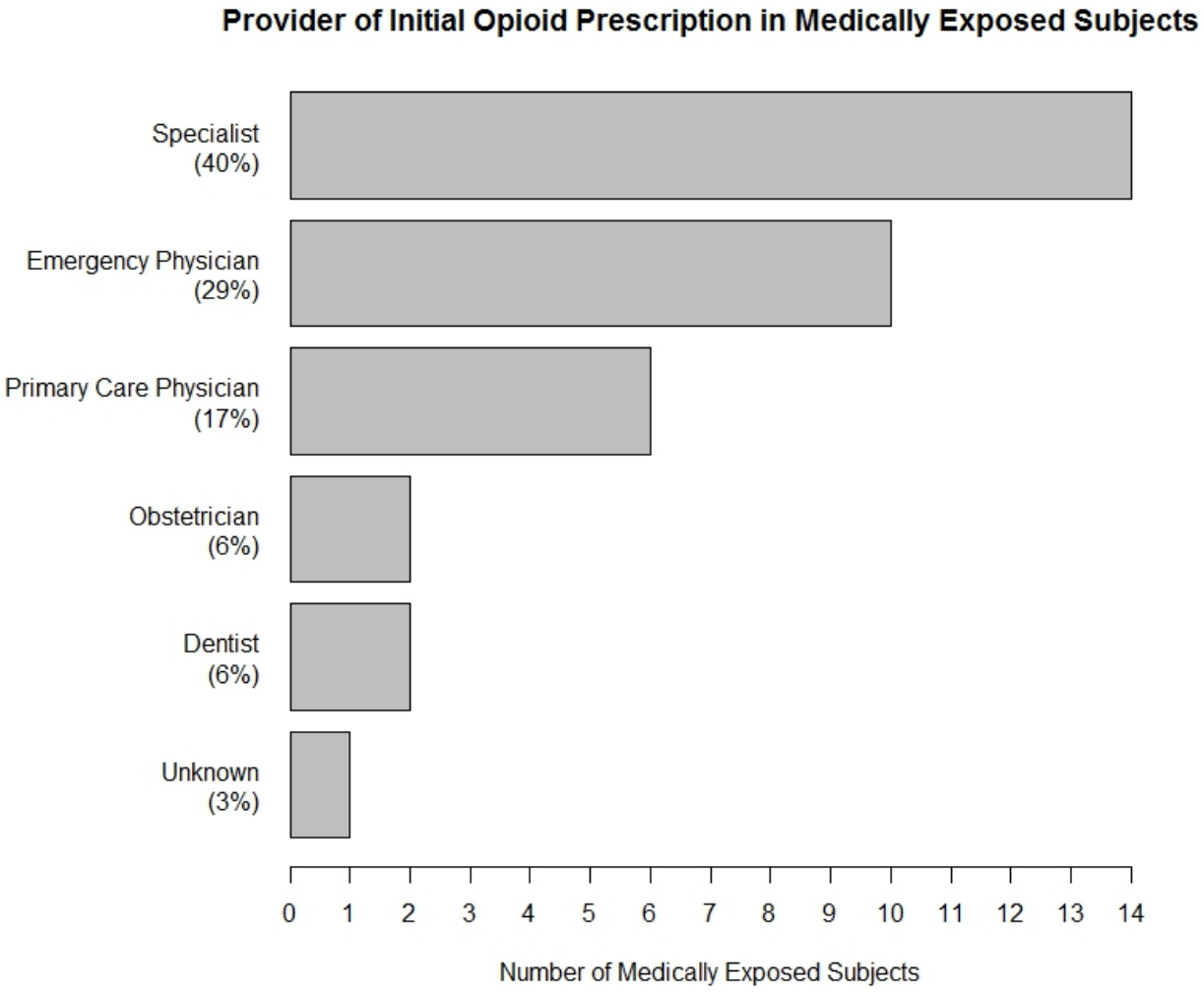

Figure 2. Sources of initial opioid prescription reported by medically exposed subjects (N=35)

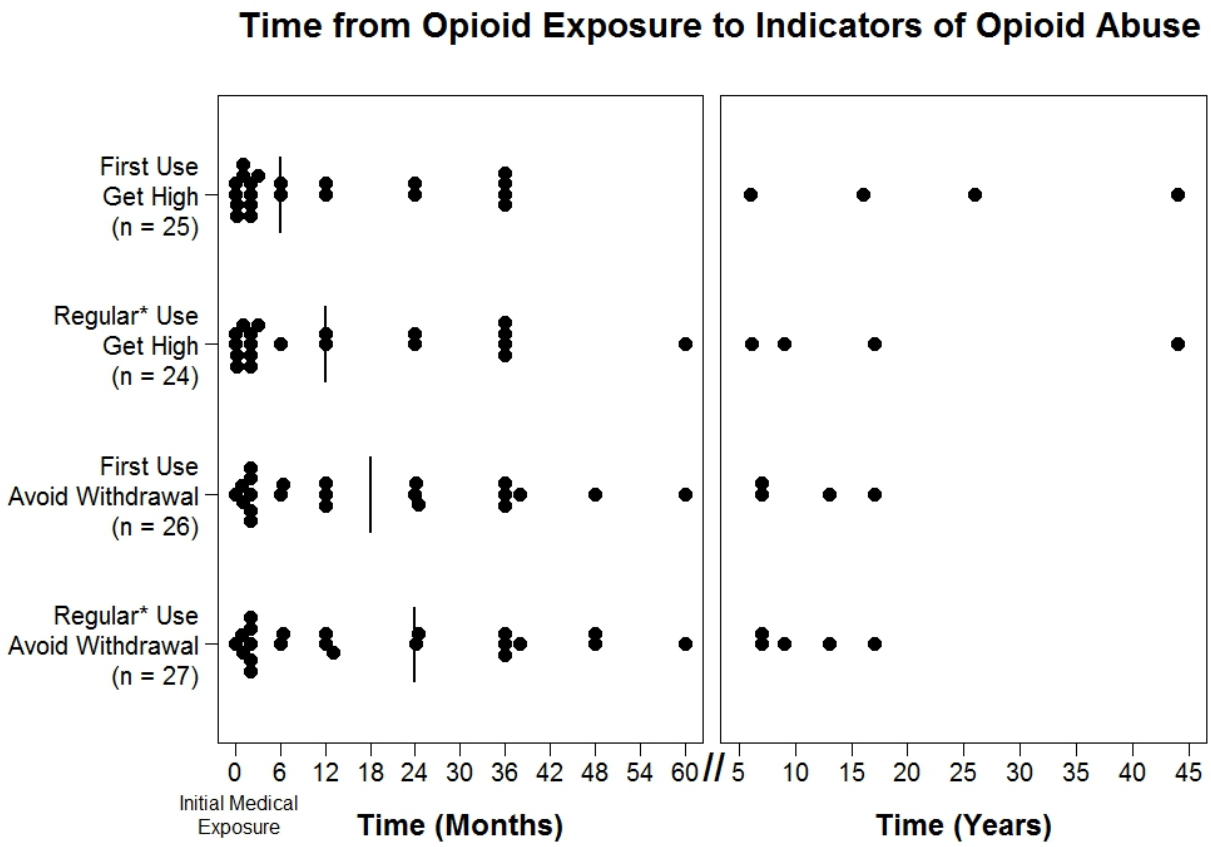

Figure 3. Time from initial opioid exposure to onset of nonmedical opioid use in medically exposed subjects, by indicator of substance abuse. Each dot represents a single case with a line representing median time from initial opioid exposure to onset of use type (N=31).

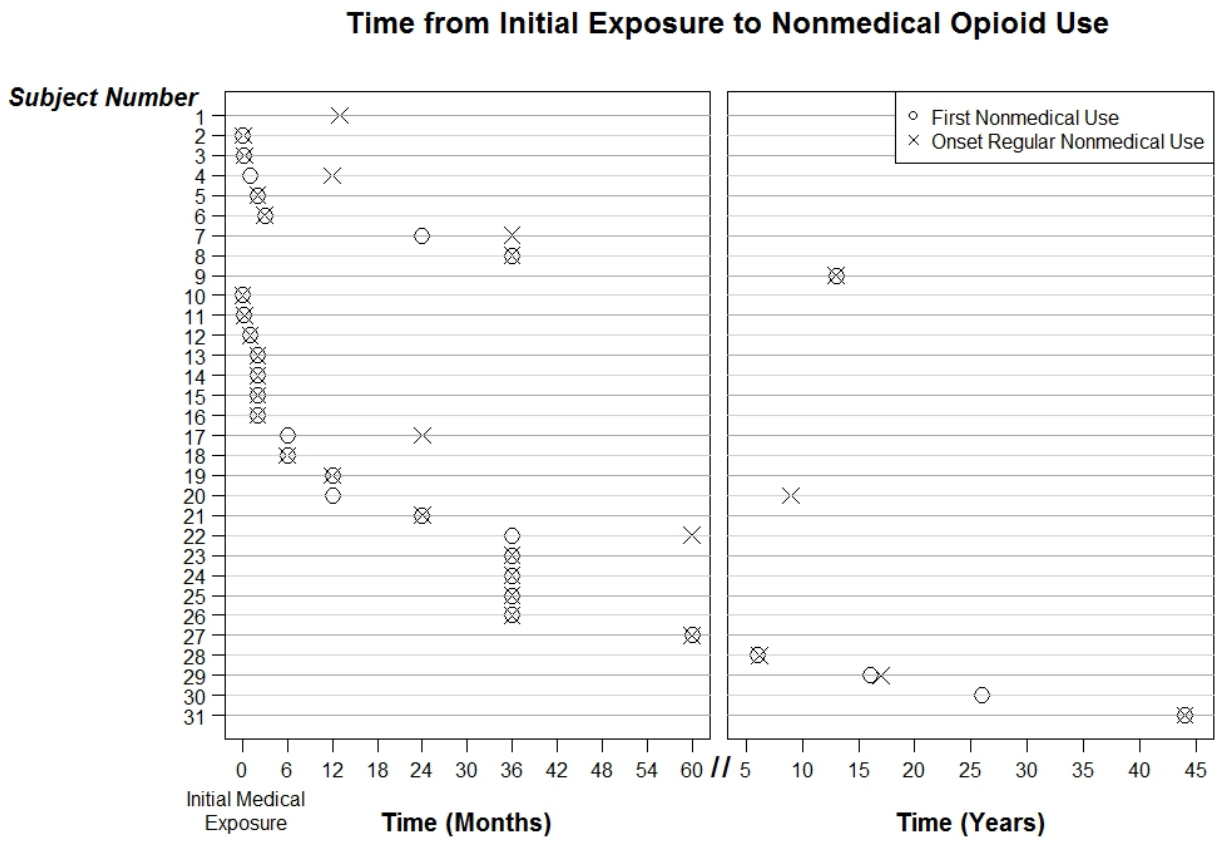

Figure 4. Time from initial exposure to onset of nonmedical opioid use and regular nonmedical opioid use in medically exposed subjects, by individual subject (N=31)

Bibliography

1. Compressed mortality file on CDC WONDER. http://wonder.cdc.gov/mortsql.html. Accessed 8/21/2014, 2014.
2. Massatti R, Beeghly C, Hall O, Kariisa M, & Potts L. Increasing heroin overdoses in Ohio: Understanding the issue. 2014. Columbus, OH: Ohio Department of Mental Health and Addiction Services.
3. Substance Abuse and Mental Health Services Administration, Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.
4. Hoppe JA, Nelson LS, Perrone J, & Weiner SG. Opioid prescribing in a cross section of US emergency departments. *Ann Emerg Med.* 2015;6(3):253-259.
5. Weiss AJ, Wier LM, Stocks C. Overview of emergency department visits in the United States, 2011. Healthcare Cost and Utilization Project: Agency for Healthcare Research and Quality, Statistical Brief #174: 2014. https://www.hcup-us.ahrq.gov. Accessed 11/16/2015.
6. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, & Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009 Apr;42(2):377-81.
7. Ancona RM, Butler MM, Beauchamp GA, Yamin CY, Winstanley EL, Hart KW, Ruffner AH, Ryan SW, Ryan RJ, Lindsell CJ, & Lyons MS. ED Prescription Opioids are a Frequent Initial Exposure Preceding Addiction. Poster presented at: University of Cincinnati Research Week; May 2015; Cincinnati, OH.
8. Ancona RM, Butler MM, Beauchamp GA, Yamin CY, Winstanley EL, Hart KW, Ruffner AH, Ryan SW, Ryan RJ, Lindsell CJ, & Lyons MS. Emergency department prescription

opioids as an initial exposure preceding addiction. Poster presented at: Society of Academic Emergency Medicine Annual Meeting; May 2015; San Diego, CA.

9. Ancona RM, Butler MM, Beauchamp GA, Yamin CY, Winstanley EL, Hart KW, Ruffner AH, Ryan SW, Ryan RJ, Lindsell CJ, & Lyons MS. Emergency department prescription opioids as an initial exposure preceding addiction [published online ahead of print November 23, 2015]. *Ann Emerg Med.*
10. IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.
11. R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.
12. Eklund A (2013). Beeswarm: The beeswarm plot, an alternative to stripchart. R package version 0.1.6. http://CRAN.R-project.org/package=beeswarm.