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ED Prescription Opioids as an Initial Exposure Preceding Addiction

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Abstract

Objective—Opioid abuse and overdose constitute an ongoing health emergency. Many presume opioids have little potential for iatrogenic addiction when used as directed, particularly in short courses as is typical of the ED setting. We preliminarily explored the possibility that initial exposure to opioids by EDs could be related to subsequent opioid misuse.

Methods—This cross-sectional study surveyed a convenience sample of patients reporting heroin or non-medical opioid use at an urban, academic ED. We estimated the proportion whose initial exposure to opioids was a legitimate medical prescription and the proportion of those prescriptions that came from an ED. Secondary measurements included 1) the proportion using non-opioid substances before initial opioid exposure, 2) the source of opioids between initial exposure and onset of regular non-medical use, and 3) time from initial prescription to opioid use disorder.

Results—Of 59 subjects, 35 (59%; 95%CI: 47-71) reported they were first exposed to opioids by a legitimate medical prescription, and for 10/35 (29%; 95%CI: 16-45), the prescription came from an ED. Most medically exposed subjects (28/35, 80%; 95%CI: 65-91) reported non-opioid

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substance use or treatment for non-opioid substance use disorders preceding the initial opioid exposure. Emergency providers were a source of opioids between exposure and onset of regular non-medical use in 11/35 (31%, 95%CI: 18-48) cases. Thirty-one of the 35 medically exposed subjects reported the time of onset of non-medical use; median time from exposure to onset of non-medical use was: 6 months for use to get high (N=25; IQR 2-36), 12 months for regular use to get high (N=24, IQR: 2-36), 18 months for use to avoid withdrawal (N=26, IQR: 2-38), and 24 months for regular use to avoid withdrawal (N=27, IQR: 2-48). Eleven (36%, 95%CI: 21-53) began non-medical use within 2 months, and 9/11 (82%, 95%CI: 53-96) reported non-opioid substance use or treatment for alcohol abuse prior to initial opioid exposure.

Conclusion—Although short-term opioid administration by emergency providers is unlikely to cause addiction by itself, ED opioid prescriptions may contribute to the development of addiction in some patients. There is an urgent need for further research to estimate long-term risks of short-course opioid therapy, so that the risk of iatrogenic addiction can be appropriately balanced with the benefit of analgesia.

Keywords

Opioids; Opiate Addiction; Iatrogenic Disease; Preventive Health Services; Emergency Service; Pain

Introduction

Background

Over the past decade, a rapid increase in the sale of prescription opioids has been directly paralleled by an increase in overdose deaths.^{1,2} Approximately 16 million people in the US report non-medical use of prescription opioids.³ In 2008, overdoses due to prescription opioids surpassed those due to heroin and cocaine combined, and drug overdose surpassed motor vehicle crashes as the number one cause of injury death for the first time.⁴ Recent increases in heroin use may be due in part to individuals transitioning from non-medical prescription opioid use to heroin.⁵

The ways in which opioid prescribing leads to harm are not well-characterized. To date, attention has focused on the problems of opioid abuse, diversion, and overdose. These issues pertain primarily to those who are already suffering from substance use disorders.⁶ More recently, the possibility that legitimate use of prescription opioids has led to incident substance use disorders (iatrogenic addiction) is beginning to gather attention.^{6,7,8,9} When iatrogenic addiction has been considered, it is almost exclusively in the context of chronic pain.¹⁰ Not surprisingly, emergency providers commonly believe that short courses of opioid therapy for acute pain are safe and that their role in the current opioid crisis is limited to attenuating diversion.¹¹ However, several recent studies have demonstrated that short course opioid therapy for acute pain is associated with future recurrent use of opioids, raising the possibility that short course opioid therapy may be a potential trigger for the onset of opioid-related substance use disorders.^{7,8,9} If so, there are considerable health implications as more than 1 in every 6 patients discharged from an ED are given a prescription for an opioid pain reliever.¹²

Importance

The risk of iatrogenic addiction must be defined before providers can balance the risk of substance use disorders with the benefits of opioids for analgesia. Demonstrating that iatrogenic addiction is relevant to the ED setting could spur research needed to identify those at risk of addiction and develop methods to modify that risk. Conversely, finding that the likelihood of iatrogenic addiction in ED patients is low could lead to improved pain treatment.

Goals of This Investigation

The goal of this study was to explore the extent to which ED patients who have come to use heroin or other opioids for non-medical purposes report that a legitimate medical prescription (i.e. prescription from their doctor used for a medical purpose) was their first exposure to opioids, and how often that prescription came from an ED. Secondly, we measured the proportion using non-opioid substances before initial opioid exposure, the source of opioids between initial exposure and onset of regular non-medical use, and the time from initial prescription to indicators of opioid use disorders.

Methods

Study design

This was a structured, investigator-administered survey study that enrolled a convenience sample of ED patients who self-reported heroin or non-medical prescription opioid use, defined as use of pharmaceutical opioids in a manner other than as prescribed. The study was approved by the Institutional Review Board.

Setting

Subjects were recruited in an urban, academic, teaching hospital serving a predominately adult population with over 70,000 encounters annually. It is the only adult Level I trauma center in the region, and it provides care for many of the region's uninsured.

Selection of Participants and Data Collection

Investigators screened for potential subjects with self-reported heroin or non-medical prescription opioid use (defined as use to get high, using more than was prescribed, or taking medication prescribed to someone else) from April, 2015 through July, 2015. This was primarily accomplished by reviewing the electronic medical record for chief complaints and triage notations including words such as heroin, withdrawal, overdose, and abscess. Potentially eligible patients could also be referred by ED staff. When no potential subjects were identified by these methods, study staff approached patients ages 18-40 to assess for eligibility by asking about medication and drug use; general medication, opioid, and drug abuse questions were mixed to disguise the actual study focus. Subjects were excluded if they were unable or unwilling to consent, had previously enrolled in the study, or were in police custody. While screening was not rigorously monitored, we did track which patients were approached and whether the approach was because of heroin use, opioid overdose, non-medical prescription opioid use, or the general screen. Potential subjects were assured

that their responses would not be directly linked to any identifiers, though identifiers were maintained in the screening log to prevent the possibility of duplicate enrollment. Structured, investigator-administered surveys (Online Appendix A) were conducted discreetly in patient rooms, with curtains drawn or doors shut, during times when others were not in the immediate vicinity.

In addition to basic demographics, the survey asked subjects: 1) age of first drug use, 2) age of first regular drug use, defined as one or more times of use per week for at least one month, 3) reasons for opioid use, 4) opioid overdose history, 5) utilization of addiction treatment services, and 6) circumstances surrounding the initial opioid exposure. Subjects reporting a legitimate medical prescription as their initial opioid exposure were asked additional questions about the source of the initial prescription and sources of opioids used between the initial prescription and the onset of regular non-medical use.

Measurements

Primary outcome measures were the proportion of subjects who reported their first exposure to opioids to have been a prescription given by the subjects' doctor which they used for a medical purpose ("medically exposed"), and of these, the proportion for whom the medication was provided by an ED.

Secondary outcome measures included: 1) the proportion with use, regular use (i.e. at least once per week for at least one month), or treatment for substance use disorder involving non-opioid substances prior to initial opioid exposure, 2) the source of opioids between initial exposure and onset of regular non-medical use, and 3) the duration of time from initial prescription to indicators of opioid use disorders, including non-medical use, regular use to get high, and regular use to avoid withdrawal.

Analysis

Analysis was descriptive. Proportions with 95% confidence intervals were calculated for the primary outcomes. Statistical analyses were conducted using SPSS 22.0, *IBM Corp*. Figures were created using R 3.0.2 and the package Beeswarm 0.1.6.^{13,14} 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 due to: heroin use (42/59, 71%), heroin overdose (12/59, 20%), and non-medical prescription opioid use (5/59, 8%). (Figure 1) Subjects had a median age of 32 (IQR: 26-39), and were primarily white (56/59, 95%), non-Hispanic (59/59, 100%), unemployed (34/59, 58%), male (33/59, 56%), and had completed high school (37/59, 63%). (Table 1)

Fifty-nine percent of subjects reported their initial exposure to opioids was a legitimate prescription from a medical provider taken as directed (35/59, 59%; 95%CI: 47-71). Of these, 10 (10/35, 29%; 95%CI: 16-45) reported their initial exposure came from an ED.

Most medically exposed subjects (28/35, 80%; 95%CI: 65-91) reported non-opioid substance use or treatment for non-opioid substance use disorders preceding the initial opioid exposure. Emergency providers were reported to be a source of opioids between the time of initial exposure and regular non-medical opioid use by 11/35 (31%, 95%CI: 18-48) subjects. (Table 1)

Figure 2 shows the trajectory from initial exposure to indicators of opioid use disorders for 31/35 medically exposed subjects who reported the time of onset of non-medical use. Figure 2A aggregates subjects by indicator of opioid use disorder, and Figure 2B depicts the trajectory for individual subjects. For most subjects the onset of non-medical use was nearly coincident or reasonably proximate to the initial exposure. Median time from exposure to onset of non-medical use was: 6 months for use to get high (N=25; IQR 2-36), 12 months for regular use to get high (N=24, IQR: 2-36), 18 months for use to avoid withdrawal (N=26, IQR: 2-38), and 24 months for regular use to avoid withdrawal (N=27, IQR: 2-48). Eleven (36%, 95%CI: 21-53) began non-medical use within 2 months, and 9/11 (82%, 95%CI: 53-96) reported non-opioid substance use or treatment for alcohol abuse prior to initial opioid exposure.

Limitations

This study was intended as a highly preliminary exploration into the question of whether emergency providers might unknowingly contribute to iatrogenic addiction. While provocative, our results are fundamentally limited and should be interpreted with caution. The study involved a small convenience sample that may not be representative of this ED or EDs in general. Opioid use between the time of initial exposure and the onset of opioid use disorder was not well-defined; an initial exposure is necessary but not sufficient for addiction. While our survey was structured, it was not validated in any way. Outcome measures are dependent on the accuracy of self-report, which is subject to recall bias at a minimum. Criteria for opioid use disorders were not assessed by standardized clinical assessment. Based on our experiences, subjects were able to report the sequence of events after initial opioid exposure, but had difficulty with precise timing of events. Social desirability bias may have contributed to inaccurate reports, though anonymity of the survey was emphasized. Finally, while our data suggest the possibility of a link, at least temporally, between ED exposures and opioid substance use disorders, our data cannot be used to estimate risk (i.e. what proportion of patients prescribed opioids in the ED will go on to develop an addiction) or determine the degree of causality.

Discussion

To date, the role of emergency medicine in the current opioid epidemic has focused almost exclusively on reducing the supply of opioids available for misuse and diversion. Though important, this only pertains to patients already suffering from opioid use disorders and does not address how those individuals first came to be involved in opioid abuse.^{6,15,16} Our study, while highly preliminary, is important as the first direct exploration of whether opioids prescribed by emergency physicians may contribute to the problem of iatrogenic addiction. We found that among ED patients with opioid-use disorders, half were first exposed to

opioids by a prescription from a medical provider, often an emergency provider, which they took as directed. That initial exposure was most frequently followed by non-medical use, use to get high, or use to avoid withdrawal within 6 to 12 months. This close temporal association raises the possibility that EDs are part of an iatrogenic contribution to incident addiction. Even the possibility that ED prescriptions can contribute to iatrogenic addiction requires urgent study, given the magnitude of the current health crisis and the frequency with which emergency providers prescribe opioids.¹²

These findings complement studies of opioid use in the year following treatment for acute pain. Clarke *et al.* found that 3.1% of opioid-naïve patients undergoing major elective surgery were still receiving opioids after 90 days.⁹ Alam *et al.* found that although the overall rate of recurrent opioid use at one year was only 8% for patients undergoing minor surgery, opioid-naïve patients who received an opioid prescription were 44% more likely to fill additional prescriptions at one year than opioid-naïve patients who did not receive a prescription.⁸ Hoppe *et al.* found that 12% of opioid-naïve patients discharged from an ED with an acute pain condition had recurrent opioid use at one year. Opioid-naïve patients who were discharged with and filled an opioid prescription were nearly twice as likely to have recurrent opioid use at one year compared to opioid-naïve patients who did not receive an opioid prescription.⁷ These retrospective studies provide important preliminary insights into the possible magnitude of risk for opioid-naïve patients, but do not clarify whether subsequent use was linked to the initial prescription or whether subsequent use was appropriate.

Our results suggest that initial opioid exposures from medical sources may be contributory to opioid use disorders. Opioid abuse and addiction do not manifest without exposure, and in many cases onset of regular non-medical use was proximate to an initial medical exposure, often occurring within 2 months. This is alarming and may indicate that the initial exposure is uniquely contributory to opioid use disorders in some cases. Such patients are likely “primed” to be unusually susceptible to the addictive potential of opioids. It is notable that over 80% of those with an early transition to non-medical use reported non-opioid substance use at the time of their initial opioid exposure. Alternatively, individuals with an early transition to non-medical use may have received an unusually high-intensity exposure (i.e. dose, agent, or duration) in the weeks following initial exposure.

Our study does not characterize the extent to which an *initial* medical exposure contributes to *eventual* opioid use disorders. Future research in this area will need to attend to questions of which exposures are contributory to opioid use disorders and the importance of initial exposures relative to subsequent exposures. Such work will be critical to developing interventions that can prevent or attenuate the development of opioid use disorders among those who are at-risk and medically exposed. Of note, the role of emergency medicine in iatrogenic addiction may not be limited to initial exposures. We found that 31% of subjects reported that the ED was a source of opioids in the time between their initial exposure and the onset of regular opioid use to get high or avoid withdrawal.

The issue of iatrogenic addiction calls into question the appropriate balance between adequate pain treatment and the potential risk of developing opioid use disorders.⁶ This risk

will vary by individual as does severity of pain. Further research into factors which may predict susceptibility to addiction could lead to the development of screening tools appropriate for the acute care environment that could help providers predict which patients are most at risk for opioid addiction. This could in turn inform risk-benefit analysis when treating pain.

In summary, more than half of patients with opioid use disorders self-reported that their initial opioid exposure was a prescription from their doctor which they took as prescribed, and of these 29% were ED prescriptions. Many of these patients began a pattern of regular opioid use shortly thereafter. While short courses of opioid medication are insufficient to cause dependence or addiction, exposure from EDs may be a contributory step in the process. This topic requires urgent investigation so that emergency providers can adequately balance the need for pain treatment with the risks of subsequent addiction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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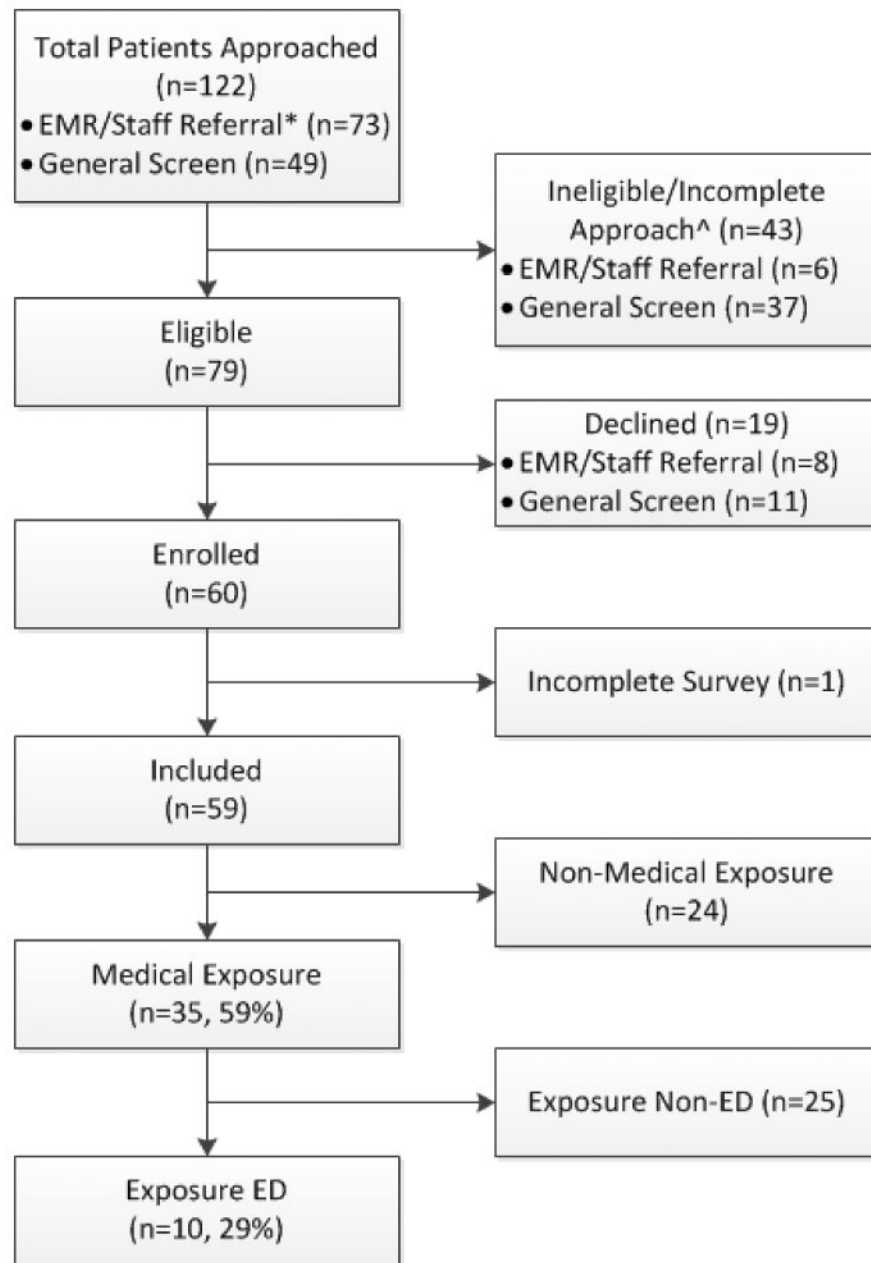


Figure 1. Flow chart of enrollment and primary outcomes

* Approach was not tracked to differentiate between EMR review and staff referral

^ Potential subjects identified through the EMR review or staff referral were ineligible if they were in police custody, under 18 years of age, or lacked capacity for informed consent; general screen potential subjects were additionally ineligible if they did not report non-medical opioid use. Approach was not complete for all potential subjects due to medical reasons or because the patient left ED prior to re-approach.

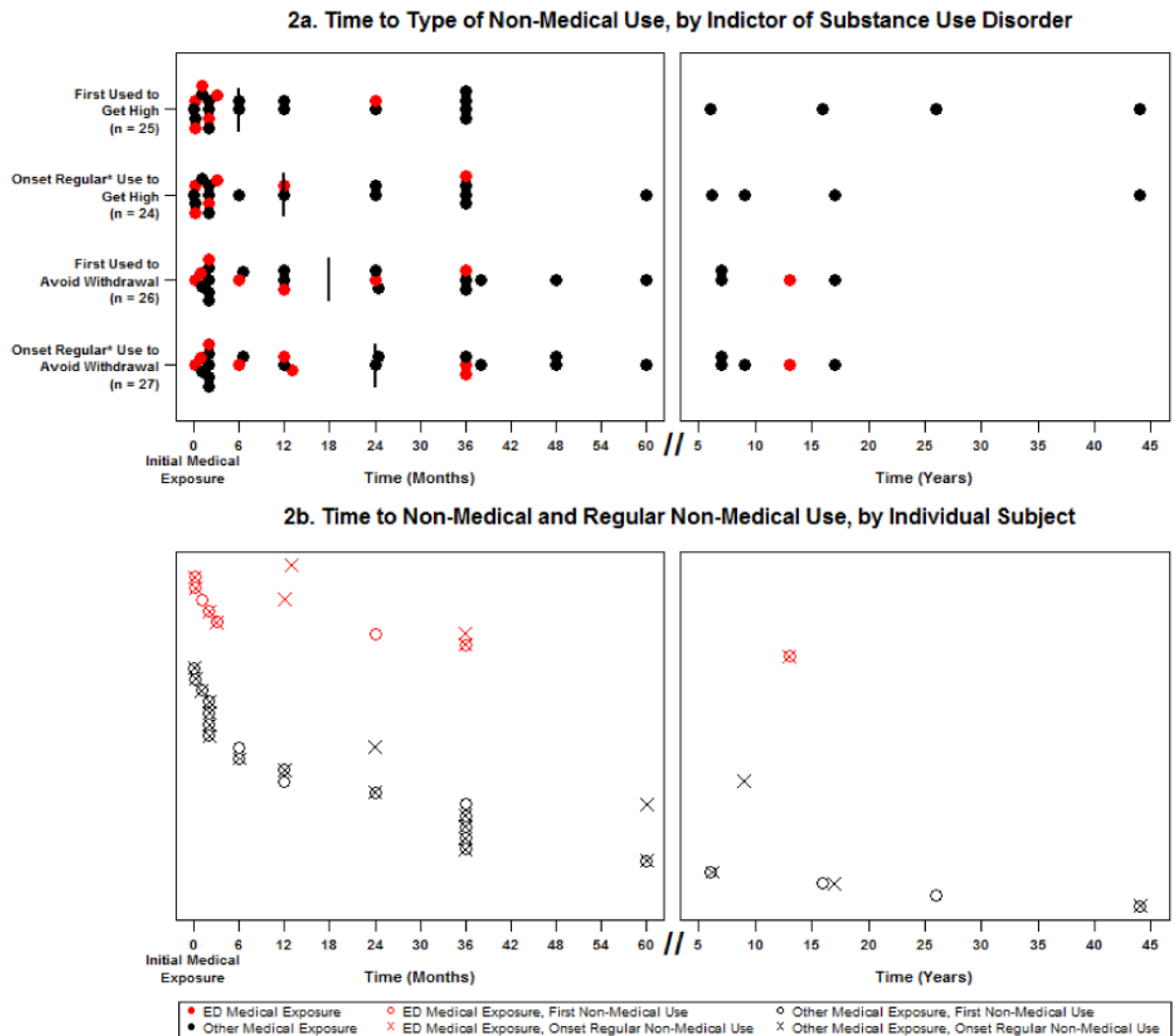
**Figure 2.**

Figure 2a shows time from initial medical exposure to types of non-medical use, organized by indicator of substance use disorder. Each dot represents a single case and each line represents the median time to each indicator. All 31 subjects reported non-medical opioid use to get high or avoid withdrawal, but not all subjects reported both. Figure 2b shows the time from initial medical exposure to the onset of non-medical use and regular non-medical use, organized by individual subject.

* Regular use was defined as using at least once a week for the duration of one month or more

Table 1
Subject demographics, non-opioid substance use prior to initial opioid exposure, and opioid sources between initial medical exposure and onset of regular non-medical use

Characteristics (Total N=59)	Medically Exposed (n=35)			Non-Medically Exposed (n=24)		
	No.	95% CI		No.	95% CI	
		(%)	LL UL		(%)	LL UL
Demographics						
Age [^]	33	(28-44)	29 37	28	(23-34)	24 31
Sex						
Male	22	(63)	46 77	11	(46)	27 65
Female	12	(34)	20 51	12	(50)	31 69
Unknown	1	(3)	0 13	1	(4)	1 18
Race						
White	33	(94)	83 99	23	(96)	82 100
Non-Hispanic	35	(100)	93 100	24	(100)	90 100
Completed High School/GED	23	(66)	49 80	14	(58)	39 76
Unemployed	21	(60)	44 75	13	(54)	35 73
Age of initial opioid exposure [^]	18	(16-27)	16 20	18	(16-20)	16 20
Subject reported opioid overdose						
Heroin	18	(51)	35 67	13	(54)	35 73
Prescription opioids	5	(14)	6 29	0	(0)	0 10
Non-opioid substance use prior to initial opioid exposure[*]						
Marijuana, ever used	25	(71)	55 84	13	(54)	35 73
Marijuana, ever used regularly ^{**}	13	(37)	23 54	9	(38)	20 57
Cocaine, ever used	9	(26)	14 42	9	(38)	20 57
Cocaine, ever used regularly ^{**}	4	(11)	4 25	6	(25)	11 45
Methamphetamines, ever used	2	(6)	1 17	3	(13)	4 30
Methamphetamines, ever used regularly ^{**}	0	(0)	0 7	0	(0)	0 10
Sedatives, ever used	4	(11)	4 25	7	(29)	14 49

Characteristics (Total N=59)	Medically Exposed (n=35)				Non-Medically Exposed (n=24)			
	No.	(%)	95% CI		No.	(%)	95% CI	
			LL	UL			LL	UL
Sedatives, ever used regularly **	3	(9)	3	21	1	(4)	1	18
Treatment for alcohol or non-opioid substance use	4	(11)	4	25	3	(13)	4	30
Opioid sources between initial medical exposure and onset of regular non-medical opioid use** (N=33)								
Drug dealer / Street	25	(76)	59	88	-	-	-	-
Emergency Physicians	11	(33)	19	50	-	-	-	-
Specialists	10	(30)	17	47	-	-	-	-
Primary Care / Clinic Physicians	5	(15)	6	30	-	-	-	-

[^] Age is expressed as Median (IQR) with 95% confidence interval of the median, missing Age for 1 medically exposed patient (n=34)

* Each subject could potentially report multiple factors (e.g. reported using both marijuana and cocaine prior to initial opioid exposure)

** Regular use was defined as using at least once a week for the duration of one month or more